



Formulations with Active Plant Molecules and Additional Therapies in Wound Healing

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Abstract

Chronic wounds are important public health issues, affecting 1.51 to 2.21 per 1000 population. These hard-to-heal wounds affect the workers, due to pain, possibility of infection, amputation, and death, impacting around 2–4% of the health budget of countries. Since ancient times, humans have used plants to treat wounds. Intensive investigation of medicinal plants, their extracts, active molecules and respective formulations begin in the first half of the twentieth century. This review aims to present the definition of wounds and their healing mechanisms; the plants and their molecules with potential to heal wounds; the main developed and patented herbal formulations; additional therapies and future trends in this field. The scientific literature on the subject was investigated in the following databases: Pubmed, Science Direct, Scopus, Lilacs, and Scielo. The Derwent Innovations platform was used for patent research. The study covered the description of wounds and the wound-healing process, medicinal plants employed in wound healing and active molecules, such as flavonoids, terpenes, polysaccharides, and proteases, along with many types of distinct formulations used to treat wounds, especially gels, creams, ointments and film membranes, and additional therapies that included skin substitutes and grafts, negative pressure wound therapy, and hyperbaric oxygen therapy. Great advancement has been observed over the main developed and patented herbal formulations based in the Green Chemistry principles. Classical formulations containing active plant molecules are commonly used to treat wounds. However, more sophisticated nanosystems and additional therapies enable important advances in the wound-healing.

Keywords Wound healing · Wound therapy · Plant extracts · Plant active molecules · Wound dressing · Nanoformulations

Introduction

A wound is a disruption in continuity of the epithelial lining of the skin or mucosa, resulting in destruction of tissues, disruption of blood vessels, and extravasation of blood constituents and tissue hypoxia. Wounds cause pain, bleeding, disability, and can lead patients to death, especially because of sepsis (Fazil and Nikhat 2020). Chronic or hard-to-heal wounds do not reduce in size for more than 40% or heal in

30 days, affecting around 1.51 to 2.21 per 1000 population in the world. This incidence is increasing with ageing populations (Zhu et al. 2022). Furthermore, the impact of social and economic of this type of wound is 2–4% of the health budget of countries (Järbrink et al. 2017).

Prehistoric humans observed that bleeding decreased on covered wounds by plants, earth and clays (Bhattacharya 2012). Therefore, they developed a multitude of wound coverings, such as ointments, certain plant extracts, herbs, or clay, which can also relieve pain and accelerate healing. For a long time, these covers were selected empirically, by trial and error. The first written record containing medical information on wound treatment with clay tablets is dated at approximately 2500 B.C., in Mesopotamia. Many plant preparations were developed by primitive people in various parts of the world (Forrest 1982). The history of the topical application of herbal medicines goes back thousands of years, with records of the Egyptian and Babylonian use of

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salves and ointments in their traditional medical systems (Khogta et al. 2020).

The pharmaceutical industry has a long history of use of medicinal plants (Tariq et al. 2022), starting with the development of chemistry, which enabled the isolation, purification and characterization of plant-based pharmaceutical ingredients (Shakya 2016). Herbal medicine is a part of traditional medicine and can be used as simple herbal preparations, containing biologically active compounds, or as medicinal plant formulations which can be applied directly to the skin, promoting the healing process. There is evidence in literature that herbal medicines are also highly effective in combating microbial diseases and are promising in the treatment of persistent infections, especially skin wound infections. The most common topically applied formulations are gels, emulsions, films and ointments, or herbal extracts themselves (Pereira and Bártolo 2016). Herbs could be applied to skin wounds in a balsam, and leaves were frequently used as bandages; many were refreshing and calming (Forrest 1982; Fazil and Nikhat 2020).

A vast number of plants have been employed in wound treatment for thousands of years. Some were astringent, such as lady's mantle (*Alchemilla vulgaris* L., Rosaceae), others presented antimicrobial activities, such as comfrey (*Symphytum officinale* L., Boraginaceae) and St. John's wort (*Hypericum perforatum* L., Hypericaceae) (Sowa et al. 2018). The usefulness of various plants in folk medicine were also suggested by their aspect; for example, the perforated leaves of *H. perforatum* suggested its application on punctures. Currently, it is known that this plant contains a diversity of secondary metabolites, such as naphthodianthrones, phloroglucinols, flavonoids, and phenylpropanoids, that have antifungal, anti-inflammatory, and antimicrobial activities, which promote the wound-healing process by increasing fibroblast proliferation, collagen bundle synthesis, and tissue revascularization (Yadollah-Damavandi et al. 2015). On the other hand, the leaves of *A. vulgaris*, which has a high content of the astringent tannin, precipitates wound proteins, forming a temporary film over the wound surface that protects it from caustic agents and microorganisms, besides promoting vasoconstriction and arrest of haemorrhage (Maver et al. 2018). Besides, *S. officinale* has allantoin and phenolic acids, which are anti-bacterial and antioxidants, being excellent healing agents due to preserving fibroblasts and inducing granulation tissue (Sowa et al. 2018).

The removal of necrotic tissue from skin wounds and burns, called debridement, is an important step in healing. Autolytic debridement is the use of products to keep the wound moist and support the gradual softening of the eschar using the natural enzymes present in wound fluid (Thomas et al. 2021). Nowadays, many molecules, especially from plants, are employed with tremendous success in the healing of all types of wounds in different formulas. This

work aims to study the concepts of wounds and their repair mechanisms, as well as to discuss the therapeutic potential of medicinal plants and their molecules in the healing of chronic or hard-to-heal wounds, since the first care for a wound is a topical formulation. However, they may need additional therapies. Therefore, we demonstrate that topical phytotherapeutic formulations, containing plants and their extracts, have been developed and patented as an accessible and effective solution in wound healing, since they have several active molecules that act synergistically. Finally, we present promising nanosystems and discuss additional treatments that are future trends in this field.

Search Strategy

The scientific literature for this review was investigated by searching Pubmed, Science Direct, Scopus, Lilacs, and Scielo databases. The research period was from 1993 to 2020. All the articles must be in English language. The keywords used were: "wound healing", "wound repair", "wound regeneration", "plants in wound healing", "plant proteases", "secondary metabolites in wound healing", "flavonoids in wound healing", "polysaccharides in wound healing", "terpenes in wound healing", "medicinal plant formulations", "wound dressing", "tissue-engineered skin substitutes", "negative-pressure wound therapy", "skin grafts" and "hyperbaric oxygen therapy" which that were present in the title or in the abstract. Articles were chosen based on more recent works, followed by the selection and analysis of articles related to the theme of the present review. The exclusion criteria were no full text available, articles not in English language, topic unrelated to articles, and articles do not peer reviewed.

Patents were evaluated using the Derwent Innovations platform along with the appropriate keywords: "plant or plants and wound", "extract or extracts and wound", "protease or proteases and wound", "flavonoid or flavonoids and wound", "polysaccharide or polysaccharides and wound" and "terpene or terpenes and wound". The results were refined for the years of 2012 to 2022, to decrease the number of patents found, and the keywords were researched in the title of each patent. All they must be in English language and with full text available.

Discussion

Wounds

Human skin is a specialized organ that acts as a primary defence barrier. It is highly adaptative and multifunctional, protecting us from the daily raid of chemicals, physical forces, and radiations that cause skin injury. Our skin is specialized to interface with the external environment and

provides sophisticated and important homeostatic functions that allow it to heal quickly and efficiently. This organ consists of 3 layers: epidermis, dermis and hypodermis. Disruptions in skin integrity led to the formation of wounds, that are classified into two major categories: acute and chronic (Wilkinson and Hardman 2020).

Generally, acute wounds heal relatively faster. During the wound-healing process, injuries occurring in the border of blood vessels lead to the formation of blood clots. In this type of wound, a cascade of cellular and biochemical events follows, directing the repair process (Rezaie et al. 2019). Chronic wounds, on the other hand, may take 3 months or even years to heal after the initial injury. Thus, chronic wounds stand as a major concern in healthcare, and their treatment is one of the most challenging issues in the field of regenerative medicine. Many factors have been related with defective wound healing, such as maceration, ischemia, and infection (Walton 2014). These types of wounds are often associated with effects of an intrinsic disease state, or flawed healing due to a coexisting disease. Types of chronic wounds include diabetic foot ulcers, pressure ulcers, venous leg ulcers, and ischemic lower-extremity ulcers. The major characteristic of chronic wounds is the lack of progression via normal stages of healing, complicating the election of a suitable treatment (Morton and Phillips 2016).

Wound Healing

As mentioned before, the skin acts as a primary defence barrier, preventing damages to internal structures. For this, it has rapid and skilled mechanisms to close discontinuities, in a process known as wound-healing response. Complete wound repair is a dynamic, integrated and complex process involving many different cell types, special molecules and events that must be firmly coordinated to efficiently repair damaged tissue, that must all occur in the appropriate sequence and time frame, and that are commonly classified into four main phases: haemostasis, inflammation, proliferation and remodelling (Wilkinson and Hardman 2020).

Haemostasis

Immediately after injury, damaged blood vessels rapidly contract and expose degraded collagen and von Willebrand factor. These proteins then interact with platelets by glycoprotein Ia and VI receptors, promoting platelet activation and adherence to the blood vessel wall, forming blood clot and preventing the severe loss of blood from vascular damage (Rousselle et al. 2019). Activated platelets are crucial in the recruitment of immune cells to the tissue injury because its granules have more than 300 biologically active substances and, they are involved in immune cell recruitment and inflammation. Platelets secrete some growth factors

that stimulate fibroblasts and keratinocytes that are crucial for wound healing, angiogenesis and remodelling. These growth factors are: platelet-derived growth factor (PDGF), which controls the growth of mesenchymal cells (fibroblasts and smooth muscle cells), stimulates collagen, glycosaminoglycan, and collagenase production by fibroblasts, promotes macrophages and neutrophils chemotaxis, and re-epithelialisation; transforming growth factor β (TGF- β), which inhibits macrophages and lymphocyte proliferation, mesenchymal stem cells proliferation, neutrophil and monocyte chemotaxis, and matrix formation; fibroblast growth factor (FGF), which has a mitogenic effect on fibroblasts, endothelial cells, mesenchymal stem cells, chondroblasts, osteoblasts, and promotes angiogenesis; epidermal growth factor (EGF), which promotes fibroblast migration and proliferation; vascular-endothelial growth factor (VEGF), which promotes angiogenesis and increases vessel permeability; and connective tissue growth factor (CTGF), which promotes platelet adhesion, white blood cell migration and angiogenesis, and regulates collagen synthesis (Golebiewska and Poole 2015).

When blood vessels are damaged, tissue factor is released to bind the blood factor VII, and the intrinsic blood cascade form the blood clot. The platelet surface is essential to activate many blood factors. Subsequently, thrombin-activated also triggers platelet activation, inducing a conformational change, reinforcing the blood clot. An insoluble clot known as eschar forms, made of fibrin, fibronectin, vitronectin and thrombospondin, and is the primary wound plug preventing bleeding. Eschars also fulfil a number of secondary functions: shielding against bacterial invasion, providing a scaffold for incoming immune cells, and reserving cytokines and growth factors to guide the behaviour of wound cells in early repair (Gantwerker and Hom 2011). As soon as enough clot is formed, the coagulation process is switched off, preventing excessive thrombosis; at the same time, the injured vessel wall is repaired by smooth muscle cells and endothelial cells (Rousselle et al. 2019).

Inflammation

The inflammation response is complex and modulated by a myriad of intrinsic and extrinsic factors that activate resident immune cells, such as mast, Langerhans and T cells, and macrophages, by binding pattern recognition receptors to activate inflammatory pathways (Martin and Nunan 2015). Afterwards, pro-inflammatory molecules, attracted by chemoattractants, including interleukin 1 (IL-1), tumour necrosis factor-alpha (TNF- α) and bacterial endotoxins, such as lipopolysaccharide (LPS), are released, attracting circulating leucocytes to the site of injury and stimulating vasodilatation, which facilitates neutrophil and monocyte adhesion, such as selectins, and diapedesis. Neutrophils, arriving early

after injury, remove necrotic tissue and pathogens through phagocytosis and the release of antimicrobial peptides, a reactive oxygen species [ROS, that are superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (HO^\bullet)], prostaglandins, and proteolytic enzymes (Wang et al. 2018).

The blood monocytes migrate to the wound tissue and differentiate into macrophages, the most important cells in tissue repair. They are activated by LPS and interferon-gamma ($IFN-\gamma$), and promote inflammation by releasing ROS, inflammatory cytokines (*e.g.*, IL-1, IL-6 and $TNF-\alpha$), and growth factors such as VEGF and PDGF. They phagocytose necrotic debris, bacteria, and apoptotic neutrophils, while also stimulating reparative processes to enable an effective wound resolution (Wilkinson and Hardman 2020). T-cells are also critical for the early injury response, being recruited in the blood to deal with the inflammation caused by the damaged tissue. Additionally, mast cells release histamine in wounds in order to aid neutrophil recruitment during early inflammation (Zhang and Zhang 2020).

Proliferation

This stage begins with fibroblast migration to the wound site, induced by PDGF, $TGF-\beta$, $TNF-\alpha$, IL-1, IL-6 and IL-2, and is characterized by the extensive activation of keratinocytes, fibroblasts, macrophages and endothelial cells to orchestrate wound closure, matrix deposition, and angiogenesis. The proliferative phase starts approximately 12 h post-injury. Keratinocytes are activated by changes in mechanical tension and electrical gradients, culminating in their migration across the wound to reform the epidermal layer, a process known as re-epithelialization. These cells remove debris and necrotic tissue from the wound bed due to the secretion of proteases, through their interactions with the structural protein of the preliminary matrix via integrin receptors. Matrix metalloproteases (MMPs), especially MMP-1 and MMP-9, are crucial for keratinocyte migration, as they help the dissociation of the integrin receptor. When keratinocytes from opposing edges meet, migration terminates, and a thin epithelial layer is established, and they suffer the terminal differentiation, to stratify and regenerate the epidermis. Besides, $TGF-\beta$ stimulates fibroblasts to create the myofibroblasts, forming thick actin bundles below the plasma membrane, which are necessary for wound contraction (Stolzenburg-Veeser and Golubnitschaja 2018). In addition to MMPs, serine proteases, such as neutrophil elastase, cathepsin G, and urokinase-type plasminogen activator, are also involved in the wound-healing process. MMPs and neutrophil elastase are often present and may persist longer in the proteolytic environment of a non-healing chronic wound (Westby et al. 2020).

Fibroblasts are the most important cells for replacing collagen, elastin, fibronectin, proteoglycans and other components of extracellular matrix (ECM), forming substantial granulation tissue. These cells degrade the provisional matrix and replace it with a granulation tissue rich in immature collagens, fibronectin and proteoglycans. This new granulation tissue enables the migration and differentiation of wound cells, supporting both the formation of new blood vessels and the deposition of mature ECM. New blood vessels are created during the process of angiogenesis to supply the metabolic demands of the highly proliferative healing tissue by the action of VEGF, $TGF-\beta$ and FGF- β . VEGF induces nitric oxide (NO) production and promotes the mobilisation of endothelial progenitor cells (EPCs) from the bone marrow into circulation. MMPs are involved in neovasculogenesis: increased NO levels promote MMP-9 secretion, helping to release EPCs from the bone marrow into circulation (Stolzenburg-Veeser and Golubnitschaja 2018).

Macrophages are also crucial in angiogenesis because they produce proteases such as MMPs, to degrade the dense fibrin network and chemotactic factors, *e.g.*, $TNF-\alpha$, VEGF and $TGF-\beta$, driving endothelial migration. Therefore, microvascular endothelial cells proliferate and migrate into the wound bed, sprouting new vessels that fuse with others to develop stable, tubular networks (Wang et al. 2018).

The skin contains a consistent network of sensory and autonomous nerve fibres, whose regeneration is essential in wound repair. Though wound innervation remains understudied, it is known that neuropeptides, such as substance P, are released from sprouting neurons and immune cells during healing, influencing various cellular processes, such as proliferation and angiogenesis (Kumar et al. 2021).

Remodelling

Fibroblasts are the major cell type responsible for ECM remodelling, replacing the initial fibrin clot with hyaluronan, fibronectin and proteoglycans, and forming mature collagen fibrils later in repair. Proteoglycans assist in the construction of mature, cross-linked collagen fibrils and help cell migration (Xue and Jackson 2015).

As healing advances, collagen type III is replaced by collagen type I, increasing the tensile strength of the forming scar. Sequential changes in the ECM require balance between collagen degradation and synthesis, obtained by temporal regulation of MMPs. These collagenases, expressed by anti-inflammatory macrophages, fibroblasts and keratinocytes, cleave local helical collagens during repair. The degradation of the normal dermal matrix causes the release of elastin fragments; elastin, being a crucial dermal component, must reform elastic fibres to retain skin elasticity. Then, myofibroblasts

bind to one another, attach to matrix fibrils, and draw the matrix together, a process called contracture. Wound repair diminishes when macrophages, endothelial cells and fibroblasts suffer apoptosis or withdraw from the injury site, leaving a scar (Reinke and Sorg 2012).

Despite the myriads of physiological responses, healing can be reduced by multiple cellular aspects of an individual that affect wound closure. This reduction is most often a result of pathological systemic changes, such as those associated with advanced age or uncontrolled diabetes. Skin wounds have a negative effect in people's lives, and their management and care generate high costs to the healthcare system every year. For that reason, many studies have been working on new approaches to skin wound healing, including investigations on potential phytopharmacological methods (Poljšak et al. 2019).

Wound Healing Plants

Since 1978, the World Health Organization recognizes the benefits of medicinal plants. The organization defines herbal agents as active compounds from plant parts or herb materials in crude or processed state, as well as excipients (WHO 2019). Phytotherapy is a field of medicine that uses plants to treat different conditions or as health-promoting agents. It is a popular method for intervention and prevention of various diseases. Around 4 billion people worldwide use plants as alternative medicine, due to their affordability, availability, and safety; nearly 80% of people living in developing countries depend on herbal medicine for healthcare, including the treatment of wounds, infectious and metabolic diseases (Ribeiro Neto et al. 2020).

As stated before, the use of medicinal plants is rooted in cultural heritage and traditionalism since ancient times. Considerable knowledge of medicinal plants has been compiled from historical documents, which were used as the basis for pharmaceutical research to discover new agents in plant extracts or fractions to accelerate wound healing (Falzon and Balabanova 2017). The use of phytotherapies grew exponentially in recent years, due to their relatively low cost, natural origin, and fewer adverse effects than chemical drugs. Numerous pharmaceuticals used in conventional medicine were originally derived from plants, such as aspirin® (acetylsalicylic acid, extracted from *Salix alba* L., Salicaceae); aceflan® (volatile oil, extracted from *Cordia curassavica* Jacq. Roem. & Schult, Cordiaceae); and imunomax® (obtained from *Uncaria tomentosa* Willd. ex Schult. DC., Rubiaceae) (Ghochikyan et al. 2014; Calixto 2019). Some examples of medicinal plants and their medicinal uses are listed in Table S1.

Wound Healing Plant Molecules

Phytotherapy is the preferred choice over conventional therapy using synthetic medicines, particularly in terms of perceived side effects, and it has been proven to be effective in skin wound healing (Ferreira et al. 2014). Traditional medicine has employed medicinal plants in many areas for millennia, and humans have learnt by experience and observation to use plants, building up an extensive traditional culture of their application (Hardy 2021). Over the last century, scientific and technical progress, and specifically molecular, metabolomic, and genomic pharmacognosy, have enabled the discovery of a large number of new molecules and their mechanisms of action, enabling the creation of a wide repertoire of medicinal plant-based medications. Whereas modern pharmacology began with the study of traditional medicinal plants, moving on to study their individual molecules and standardised extracts, modern pharmacognosy focuses on improving research and discovering new properties and assaying the potency of an increasingly large number of medicinal plants by high-throughput screening, target-based drug discovery, and in silico methods for virtual ligand screening (Colalto 2017).

In modern science, plant species that are traditionally used to cure diseases have been extensively studied for the identification of their bioactive constituents and development of new drugs. Studies concerning mechanisms of action and effectiveness have shown that many of these plant compounds are pharmacologically safe, suggesting additional tests should be carried out in preclinical studies and clinical trials (Atanasov et al. 2021). Besides, a significant portion of the world population cannot afford industrialized medicines, and the use of herbal remedies can benefit these patient groups (Lordani et al. 2018).

Secondary plant metabolites have been essential in the discovery of new potential wound-healing agents, since these molecules offer an alternative to aid this process. Experimental evidence and many surveys sustain that plant molecules have beneficial properties on wound healing, as well as on various types of skin diseases (Moeini et al. 2020). The effectiveness of their active principles for wound treatment has been recently observed by many biochemical, molecular and pharmacological investigations. Volatile oils from *Lavandula*, *Croton*, *Blumea*, *Pinus*, *Cedrus*, *Abies*, *Eucalyptus*, *Cymbopogon*, *Rosarinus*, *Origanum*, *Salvia* and *Plectranthus* species demonstrated faster closure wound size, improved collagen deposition and higher fibroblasts proliferation (Pérez-Recalde et al. 2018). Many volatile oils are associated with biopolymers, such as gelatine, collagen, alginate, chitosan, elastin and dextran, creating nanofibrous dressings with antioxidant, anti-inflammatory or antimicrobial activities (Huesca-Urióstegui et al. 2022).

Organic, aqueous and hydro-alcoholic extractions have been the primary approach to obtain active ingredient molecules from plants. Alerico et al. (2015) demonstrated that an ethanolic extract of *Achyrocline satureioides* (Lam.) DC., Asteraceae, containing flavonoids, coumarins, phenolic acids and polysaccharides, had antimicrobial and anti-inflammatory properties and improved fibroblasts and keratinocytes proliferation. Ponnusamy et al. (2015) observed beneficial effects in wounds using a rich polyphenol fraction from *Dicranopteris linearis* (Burm. f.) Underw., Gleicheniaceae, that increased fibroblast proliferation and migration. Finally, methanolic extract from *Pongamia pinnata* L. Merr., Fabaceae, leaves, rich in alkaloids, flavonoids, steroids and glycosides, demonstrated antimicrobial and antioxidant effects in skin ulcers, wounds, inflammations and infections (Dwivedi et al. 2017).

Flavones and Flavonoids

Flavonoids form one of the major groups of specialized metabolites or secondary metabolites. Today, more than 6,000 different compounds have already been described in nature, specially from plants (Luna et al. 2020). They can also be classified as polyphenols, because they often have one or more hydroxyl substituents in their structure, that also have a flavan nucleus of 15 carbon atoms (C₆-C₃-C₆) and are diphenyl-propanoids (Salehi et al. 2019). In plants, these compounds perform a great diversity of functions, such as regulating cell growth, attracting pollinator insects, protecting against biotic and abiotic stresses, UV filtration, interfering with signalling pathways and gene expression, ROS scavenging (antioxidant), as anti-inflammatories, and having many roles in heat, drought, and frost tolerance (Dias et al. 2020, 2021). They stand out for being generally abundant in natural extracts, and different flavonoid classes have been studied as wound-healing treatment alternatives, and some examples of which are outlined below.

A chitosan hydrogel containing a flavonoid fraction from *Passiflora edulis* Sims, Passifloraceae, leaf extract demonstrated a beneficial effect on the treatment of skin lesions in diabetic rats, especially in the first few days after injury. This hydrogel was able to stimulate the antioxidant defence system, resulting in a potential formulation to be employed as dressings in the treatment of diabetic wounds (Soares et al. 2020).

The extract from French maritime pine tree (*Pinus pinaster* Aiton, Pinaceae) had shown, in experimental and *in vitro* studies, to exert photoprotective, antimicrobial, antioxidant, anti-inflammatory and anticarcinogenic effects, which were associated to its proanthocyanidin content. These molecules present high affinity to collagen and elastin and are able to inhibit the enzymatic hydrolysis by MMP *in vitro*. *In vivo* studies demonstrated that applying the extract over

wounded tissues significantly reduced wound size, due to the presence of these flavonoids (Dogan et al. 2017).

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a well-known flavanol, with anticancer, antiproliferative, anti-inflammatory, antibacterial and antioxidant activities. Several studies have demonstrated its important effect in wound healing (Kim and Park 2020; Hofer et al. 2020). Özay et al. (2019) reported wound repair and regeneration action in diabetic excisional and nondiabetic incisional wounds treated with 1% (w/w) of kaempferol ointment for 14 days. The wound showed higher levels of hydroxyproline than those in the control groups. This hydroxylated amino acid is found in abundance in collagen and elastin structures and is an important re-epithelization indicator.

Quercetin is a polyhydroxy flavonoid frequently found in flowers, leaves, and fruits of various plants. It has various pharmacological activities, such as being anticancer, anti-oxidation, anti-fibrosis, and anti-inflammatory, and therefore has high medicinal value (Xu et al. 2019; Salehi et al. 2020). It proved to be a good tool in wound repair management in different wound-healing conditions due to the presence of catechol and hydroxyl groups, that can neutralise free radicals escaping from the skin's endogenous antioxidant system, consequently inhibiting lipid peroxidation (Ozgen et al. 2016). Topical application of quercetin was also able to increase fibroblast proliferation, while decreasing fibrosis and scar formation and increasing the glutathione levels preventing the generation of novel ROS. Besides, it can chelate metal ions that could catalyse ROS formation (Fu et al. 2020). Vale et al. (2021) reported that pectin and casein microcapsules containing quercetin had an enhanced topical efficacy in blocking UVB-induced biochemical, cellular and pathological changes in the skin. Topical 3% quercetin ointment w/w demonstrated to be effective in accelerating wound repair by increasing collagen deposition and cell proliferation, due to modulating cytokines and growth factors. Besides, daily topical application of this quercetin ointment on diabetic wounds for 21 days resulted in increased expressions of interleukin-10 (IL-10), VEGF and tissue growth factor-b1 (TGF-b1) and decreased the expressions of tumour necrosis factor- α (TNF- α), IL-1b, MMP-9. The modulations of these cytokines, growth factors and proteases led to granular tissue formation, suppression of persistence of inflammatory cells, fibroblast proliferation, angiogenesis, thick collagen fibre synthesis, axonal regeneration, and faster regeneration of the epithelial layer, all of which significantly reflect the improvements in repair and regeneration of diabetic wounds in rats (Kant et al. 2020, 2021). Other findings indicate that quercetin reduces the production of inflammatory mediators such as IL-6, playing a role by inducing hemeoxygenase-1 (HO-1) and destroying the activation of inflammatory signalling pathway components,

thereby modulating macrophage polarization from M1 to M2 phenotype and further inhibiting inflammation, accelerating diabetic wound repair (Fu et al. 2020).

Apigenin naturally occurs as 4',5,7-trihydroxyflavone, and exists as apigenin-7-*O*-glucoside and various acylated derivatives. It is one of the most widespread flavonoids in plants, with countless nutritional and organoleptic characteristics, belonging to the flavone sub-class. Plants belonging to the *Apium*, *Artemisia*, *Achillea*, *Hypericum*, *Matricaria*, and *Tanacetum* genera are the main sources of this compound (Shankar et al. 2017). The large number of studies indicate that this flavone has many interesting pharmacological activities and nutraceutical potential. Apigenin was proved to be an antioxidant and can also be an important therapeutic agent for inflammation, autoimmune and neurodegenerative diseases, and even several types of tumours (Salehi et al. 2019). Topical treatment with Apigenin gel demonstrated to improve the degree of reepithelialisation and inflammation and favoured neo-vascularisation of the wounds (Lopez-Jornet et al. 2014). Besides, extracts from *Matricaria chamomilla* L., Asteraceae, and *Punica granatum* L., Lythraceae, which have high apigenin content, induced wound contraction and accelerated wound closure more than the conventional treatment with chemical compounds (Niknam et al. 2021).

Terpenes and Terpenoids

Isoprenoids are one of the largest and most diverse group of natural compounds, mostly found in plants, totalling more than 55,000 molecules described, and are a rich reservoir of candidate compounds for drug discovery. They are classified according to the organization and number of five-carbon (isoprene) units it contains, including hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), and polyterpenes ($> C_{30}$). These compounds have been employed in cancer chemotherapy and have antimicrobial, antifungal, antiviral, antihyperglycemic, anti-inflammatory, antioxidants, antiparasitic, and immunomodulatory effects. However, many terpenes are found in low levels in nature (Cox-Georgian et al. 2019).

Carvacrol and thymol are important monoterpenes found in volatile oils of species from the *Origanum* genus and are investigated regarding their application as wound-healing agents. Carvacrol incorporated to chitosan films (0.5 or 1%) had a potential use on skin wound healing by promoting granulation tissue formation and enhancing cell epithelization and proliferation in rats, leading to reduction of oedema and wound areas (Costa et al. 2019). Volatile oils containing thymol and carvacrol modulate the production and release of reactive species, such as NO, pro-inflammatory cytokines and growth factors involved in the primary stages of the

repair process. Besides, carvacrol inhibits the expression of different types of cytokines, such as IL-4, IL-17, IL-1 β and TNF- α , and the isoenzyme cyclooxygenase 2 (COX-2), but also increases IL-10, a crucial anti-inflammatory cytokine (Cicalău et al. 2021; Dantas et al. 2021). Injury treatment with thymol showed a promotion of type III to type I collagen replacement in 14 days. Also, both isomers were able to downregulate MMP-9 and MMP-2, suggesting a complete collagenation and favourable regeneration, indicating it is an interesting alternative in the management of chronic wounds (Lv and Chen 2017; Costa et al. 2019).

The volatile oil of *Bursera morelensis* Ramírez, Burseraceae, demonstrated promotion of fibroblast migration, which leads to collagen production and remodelling, indicating an alternative use for scars with tensile strength. This activity was associated with the presence of important anti-inflammatory terpenes found in the volatile oil of *B. morelensis*, α -pinene and α -phellandrene (Salas-Oropeza et al. 2020). It was demonstrated that α -pinene has anti-inflammatory activity for decreasing COX-2 production and inhibiting TNF- α , IL-1 β and IL-6. Further, α -phellandrene also inhibits the production of TNF- α and IL-6 and revealed antinociceptive effects. Moreover, both molecules induce cell cycle arrest and cell apoptosis, and are able to accelerate wound closure and promote collagen deposition (Salas-Oropeza et al. 2021).

Polysaccharides

This is a group of complex carbohydrates, ubiquitous high-molecular weight polymers that occur widely in nature. They are formed by repeated monosaccharide units joined by glycosidic bonds (Imre et al. 2019). These saccharides are extensively used in various healthcare products and medicines for their notable biological activities, such as antimicrobial, antioxidant, antitumor and neuroprotective effects. They are among the natural biopolymers found on Earth which are widely used as biomaterials for wound healing and tissue engineering (Gao et al. 2018). Acemannan is the major bioactive polysaccharide of *Aloe vera* (syn. of *Aloe succotrina* Weston, Asphodelaceae), which is extracted from the plant's gel and skin. This molecule has been reported to have many pharmacological and biological applications in medical and industrial areas (Sierra-García et al. 2014). Recently, acemannan has been investigated for employment in the treatment of wounds and alveolar osteitis, using protocols approved by the US Food and Drug Administration (Liu et al. 2019). This polysaccharide was found to induce oral wound-healing functions in human gingival fibroblasts. This effect could be explained because acemannan stimulated the expression of collagen production by keratinocytes. A clinical trial showed that a skin patch of 5% acemannan reduced ulcer size and pain (Xing et al. 2015).

Another plant polysaccharide was isolated and purified from the rhizomes of *Curcuma zedoaria* (Christm.) Roscoe, Zingiberaceae, and promoted wound contraction, re-epithelialization, dermal angiogenesis, and collagen synthesis and deposition in diabetic rats, speeding up wound repair (Xu et al. 2018) Another polysaccharide, purified from roots of *Sanguisorba officinalis* L., Rosaceae, also demonstrated efficiency in experimental and mice burn wounds by accelerating wound contraction, decreasing the epithelialization period and hydroxyproline content, and promoting collagen synthesis and angiogenesis (Zhang et al. 2018a, b).

Proteases

All living organisms have several types of proteases or peptidases in all parts of their cells, which irreversibly cleave peptide bonds in proteins, polypeptides and peptides, in different environments and under different conditions. They have important therapeutic applications in certain diseases and conditions and are named as therapeutic enzymes, which are enzymes used in the treatment and diagnosis of diseases, and also in surgical procedures (Silva-López and Gonçalves 2019).

At the end of last century, proteases were initially used as therapeutic agents in haemostasis disorders such as coagulation factors VIII and IX to treat, respectively, haemophiliacs A and B, and urokinase, which converts plasminogen into plasmin, which in turn degrades fibrin polymers, being used in cases of thrombosis. These enzymes were obtained from natural sources, human and animal plasma, but large amounts of material were required to obtain a small amount of these enzymes. In addition to the low yield of these proteases, there was the imminent risk of contamination of the source material with pathogenic infectious agents, which could cause secondary infections and immunological reactions in patients who received them (Wolberg et al. 2012). Nowadays, they are produced by recombinant DNA technology, where the gene encoding of interesting proteases are inserted into suitable expression vectors and overexpressed in specialized vectors according to the complexity of the protein. Then, they are purified, standardized and finally formulated for human or veterinary use. Although it is a complex and expensive procedure, it guarantees quality and absence of pathogenic infectious agents (Swiech et al. 2017). However, therapeutic plant proteases are not heterologous proteins. They are obtained directly from the plant organs or latex, and it is possible to extract them without affecting the plant viability. These proteases are structurally simple and relatively easy to obtain, at low cost of production (Matagne et al. 2017). They are widely used as therapeutic enzymes in the treatment of wound healing, cancer, digestive disorders and infectious diseases (Rathnavelu et al. 2016; Ferreira and Silva-López 2021).

Wound repair is majority mediated by MMPs and serine proteases. In normal wound healing, proteases are active in all phases, via a cascade of precisely regulated steps and events that align with the appearance of various cell types in the wound bed during four distinct phases: haemostasis, inflammation, proliferation and epithelialization/remodelling. They are necessary for removal of denatured collagen, elastin, fibronectin, proteoglycans and other proteins from damaged matrix (debridement), contraction of the ECM, migration of epidermal cells, and remodelling of the scar (Westby et al. 2020). The most important therapeutic plant proteases employed in wound repair are bromelain and papain, which are discussed hereafter.

Bromelain is a crude aqueous extract rich in cysteine proteases obtained from the stem and fruit of species of the Bromeliaceae family, of which the pineapple (*Ananas comosus* (L.) Merr. and *Ananas sativus* Schult. & Schult.f. (syn. *Ananas comosus* var. *comosus*)) is the better-known species. The non-proteolytic constituents of this extract are escharase, glycosidases, peroxidases, ribonucleases, cellulases, carbohydrates, protease inhibitors, and other substances (Varilla et al. 2021). The escharase is a nonproteolytic enzyme with 45 kDa, that has no hydrolytic activity against normal protein substrates, but is responsible for debridement of necrotic tissue. It helps in the digestion, dissection and separation of non-viable, devitalized tissue, especially eschar (Silva-López 2017).

Pineapple tissues contain at least four proteases that belong to the papain superfamily: stem bromelain (EC 3.4.22.32), fruit bromelain (EC 3.4.22.33), ananain (EC 3.4.22.31), and comosain. They represent the whole protease activity of bromelain that showed expressive stability at high temperatures. Bromelain is prepared from pineapple juice by centrifugation, ultrafiltration, and lyophilization, yielding a yellowish powder, and the protease activity is determined (Rathnavelu et al. 2016). Pineapple (chemically known since 1876) has been used as a medicinal plant by many cultures, and its medicinal properties are attributed to bromelain (Petrovska 2012). Because of its complex composition, this extract interacts with many host molecules and provides a great diversity of pharmacological effects. Bromelain has been used for the treatment of many diseases and conditions, such as rheumatoid arthritis, thrombophlebitis, wounds, bronchitis, sinusitis, and for enhancing the absorption of certain drugs. In all these situations, this extract expressively alleviates pain and swelling, and decreases the healing time required with conventional treatments (de Lencastre Novaes et al. 2016; Tap et al. 2016). Bromelain decreased inflammatory mediators and was an anti-inflammatory agent in various conditions, since it modulated surface adhesion molecules on T cells, macrophages, NK cells and induces secretion of IL-1 β , IL-6, TNF- α . Besides, it has analgesic properties,

since it decreased the levels of pain mediators PGE2 and bradykinin (Varilla et al. 2021).

Debridement is the procedure of removing dead, infected, senescent, and/or devitalized tissues, because they interfere in the healing of a wound. This procedure transforms a chronic wound into an acute one and reduces the bacterial burden. The bromelain proteases degraded necrotic debris and regulated cell maturation and multiplication, collagen synthesis, and development and removal of perivascular fibrin. They also hydrolysed collagen, elastin, laminin, fibronectin and other damaged components of the ECM, releasing the growth and angiogenic factors sequestered in this matrix, activating bioactive chemokines and cytokines (Silva-López 2017). The extract promoted the effective repair of wounds. The topical formulations containing 35% bromelain also contains escarase, which efficiently removed eschars. Debridement accelerated recovery of blood perfusion, controlled the expression of TNF- α , which provides a chemotactic gradient for additional leukocytes to enhance the inflammatory process, stimulates cytokine secretion, and enhances fibroblast and smooth muscle cell chemotaxis, reprogramming the wound microenvironment (Wu et al. 2012; Anghel et al. 2016). Bromelain debridement is much better than the surgical procedure, because the surgical incision is painful, non-selective, and exposes the patients to the risk of repeated anaesthesia and bleeding. Bromelain debridement reduced the time to complete wound healing and reduces morbidity and mortality of severely burned and infection patients (Krieger et al. 2016).

Papain (EC 3.4.22.2) is a cysteine protease obtained from the latex of *Carica papaya* L., Caricaceae, a tropical fruit known as papaya. The papain activity is related to the fruit maturation: the greener the fruits, the greater the protease activity. It was the second protein to be crystallized (1968) and is also a model of the papain-like cysteine protease family and helps in understanding the action mechanism of cysteine proteases (Liu et al. 2018). This protease has high activity, important stability at high temperatures, and concentrations of organic solvents/denaturant agents at a wide pH range (3–9), beside it is easy to purify (dos Anjos et al. 2016). Papain is used in pharmaceutical preparations in the treatment of many disorders (Xue and Jackson 2015). It was employed with great success in tissue debridement and wound healing in ulcers, such as pressure, diabetic, leprosy and chemotherapeutic ulcers, in Fournier's syndrome, and other injuries. Papain was able to produce proteolysis in necrotic tissues and cell fragments, helping to join wound edges and accelerating tissue regeneration (Craik et al. 2011). In addition, papain also reduced wound pH, stimulating the production of cytokines that promote cell repair, and decreasing the growth of microorganisms and inflammatory responses (Azevedo et al. 2017).

Medicinal Plant Formulations

Simple herbal preparations can be used to heal many kinds of wounds, as the herbal extract itself, or can be administered to the skin as medicinal plant formulations, usually gels, emulsions, membrane films and ointments as stated in Fig. 1 (Anvisa 2011; Pereira and Bártolo 2016).

A gel is a semi-solid dosage form that contains a gelling agent to provide viscosity to a system in which colloidal-sized particles are uniformly distributed. Gels can be defined as a dosage form containing liquid phase constrained in a polymeric network held together by physical or chemical interactions, and capable of absorbing water or biological fluids to swell. Pharmaceutical gels contain medicinal, cosmetic or other agents, with sizes varying from nanometres to micrometres (Bolla et al. 2018). It can have a hydrophilic or hydrophobic character, depending on the base used in its composition. Hydrogels are three-dimensional networks formed by natural or synthetic polymers (*e.g.*, collagen, chitosan, hyaluronic acid) which have high water content. The literature contains numerous studies of hydrogel dressing formulations aimed at wound healing, especially for chronic wounds, as they avoid microbial contamination but allow air and water vapor to reach the skin, not being occlusive (Thapa et al. 2019). However, the high-water content does not allow them to absorb a large number of exudates, and they are not suitable for treating very exuding skin wounds (Sarabahi 2012).

Polymeric films and membranes can be classified by their dense, porous or fibrous structure, often intended for topical application aimed at wound healing, which makes them useful as dressings (de Souza et al. 2020). This type of structure is widely used as a scaffold to support cell growth in tissue engineering as well; sometimes, in combination with

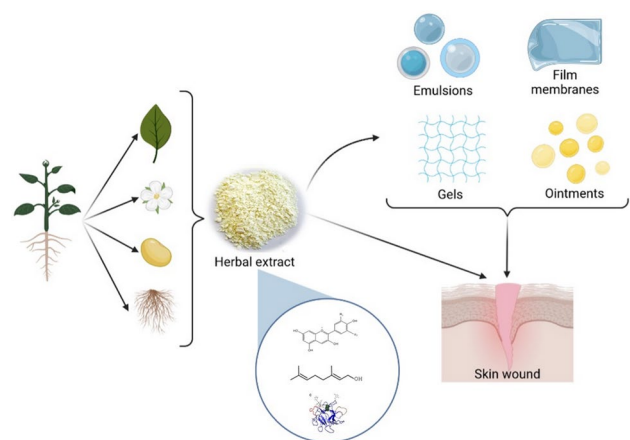


Fig. 1 Herbal extract, containing active molecules, and medicinal plant formulations, as gels, ointments, emulsions, and film membranes are usually administered to the skin to treat wounds. In the circle is showed a flavonoid, a terpenoid, and a protein structure

engineered layers, it can improve mechanical properties and decrease the permeability of microbial contaminants. They have high load capacity, can be used for direct drug delivery to the wound site, and are usually permeable to gases and impermeable to liquids and bacteria. The films are flexible, which allows for easy accommodation to the patient's body, even in difficult areas such as joints, and endorse wound inspection without removing the dressing (Savencu et al. 2021). Nanofibers are highly valued in the field of wound healing because they can replicate the extracellular matrix structure in skin tissue, which cannot be fully achieved using traditional wound dressing materials (Juncos Bombin et al. 2020). Foam dressings are usually made of highly absorbent polyurethane, creating a moist environment and providing wound isolation. They are non-adherent, easy to apply and remove, and are intended for highly exuding wounds (Sarabahi 2012).

Ointments are semi-solid, spreadable and homogeneous bases that are used for external application on the skin or mucous membranes. From a pharmaceutical point of view, ointments are clearly distinguishable from creams and gels, as they consist of only one phase in which solid or liquid substances can be dispersed. Classic ointments are hydrophobic in nature, poorly absorbed, and traditionally used for local and topical application of medications, such as wound-healing agents (Osborne 1993). The mechanism for wound healing can be associated with the petroleum base used in the composition of the ointment, which can decrease epithelial proliferation (Uetsu et al. 2002). Due to their semi-occlusive character, ointments are not suitable for all biomedical applications, and some studies suggest that other topical therapies may have better benefits in tissue healing (Leise 2018; R  ther and Voss 2021). A cream is a semi-solid pharmaceutical form that consists of an emulsion, formed by a mixture of a lipophilic phase and a hydrophilic phase stabilized by the presence of a surfactant, and is normally used for external application on the skin or mucous membranes (Jaiswal et al. 2014). Like ointments, creams can present a degree of occlusion in wounds.

As reported before, some plants and their parts are popularly employed in the treatment of wounds. Here, examples of herbal formulations described in the scientific literature with potential to heal skin wounds are summarized.

Gels based on papain have antibacterial and anti-inflammatory activities and constitute a non-invasive technique for wound repair (Pinto et al. 2007). Topical formulations have been developed, such as hydrogels using carboxyvinyl polymer and oil-in-water (o/w) emulsions, containing papain for wound healing. The glycolic extract of *Ananas comosus* is usually administered as a gel, cream and lotion as its final dosage forms.

Aloe vera is traditionally one of the most used herbal medicines in topical formulations to heal skin lesions, being

the most suitable for healing burn wounds (Maenthaisong et al. 2007). *Aloe vera* has been used in the preparation of pharmaceutical products, including hydroalcoholic gels prepared with its glycolic extract, 50% glycol extracts, simple *A. vera* ointments, tablets and capsules (Anvisa 2011).

Matricaria chamomilla is commercially available in the form of ointments containing the fluid extract of 10% *M. chamomilla* or tinctures (Martins et al. 2009; Yadav et al. 2021). A species of chamomile is marketed as a cream under the name Kamillosan® for healing skin lesions (Maver et al. 2015).

Avena sativa presents anti-inflammatory and healing activity, and its colloidal extracts are widely used in commercial formulations such as ointments, creams, gels, shampoos and soaps (Maver et al. 2015).

The main topical formulation with *Ginkgo biloba* L., Ginkgoaceae, consists of plant extracts applied directly to the injured tissue, but there is also scientific research with innovative formulations, such as carbomer gels, containing the herbal medicine carried in vesicles such as liposomes (Zhang et al. 2020).

Calendula officinalis L., Asteraceae, is usually administered as oils, infusions, tinctures, liquid extracts, creams or ointments (Maver et al. 2015; Gunasekaran et al. 2020). *Camellia sinensis* (L.) Kuntze, Theaceae, is commercially available as vegetable oil (Yadav et al. 2021).

In traditional Iranian medicine, people apply *Citrus limon* (L.) Osbeck, Rutaceae, leaves directly to the skin to treat skin wounds. Probably, the therapeutic properties of *C. lemon* are associated to its antioxidant compounds (Abbasi et al. 2021).

Curcuma longa L. is a phytotherapy species widely used in Asia. It is usually found in the form of talc and ointments and used in the treatment of chronic wounds, as it has antimicrobial, anti-inflammatory, antiviral and antifungal activities (Fazil and Nikhat 2020). There are formulations of pastes, ointments and powders containing the plant rhizome (Maver et al. 2015).

The scientific literature also reports the development of several new active release and targeting systems, aiming to improve some parameters related to plant-based pharmaceutical ingredients such as minimizing degradation and loss, preventing harmful side effects, improving the fraction of plant-based pharmaceutical ingredients accumulated in the necessary amount at the site of action, and increasing the bioavailability of the active. Among phytotherapy drug carriers, we can mention the development of soluble polymers, microparticles made of biodegradable and natural or synthetic polymers, microcapsules, lipoproteins, liposomes and micelles (Devi et al. 2010). Innovative formulations such as biocompatible membranes have been developed by numerous research groups reported in the literature. Skin wounds have been treated with great success with polymeric

membranes of polylactic acid and babassu oil, developed through techniques such as electrospinning (Fernandes et al. 2021).

Due to its enormous therapeutic potential, recent research involving *A. vera* is focused on obtaining maximum benefits from this species (Maan et al. 2018). Various types of formulations, such as functional films, hydrogels and sponges, are being developed, mainly by combining the species with various biopolymers, such as cellulose, gel gum, alginate, chitosan or gelatine, in order to optimize its wound healing property (Maan et al. 2018). A gel formulation containing *A. vera* and insulin nanoemulsion developed for wound healing was tested in diabetic rats (Chakraborty et al. 2021).

Dutra et al. (2017) developed films for dressings containing papain, aiming at cellular healing. Ahlawat et al. (2019) reported the fabrication of new polyvinyl alcohol and gelatine nanofibers loaded with *C. papaya* by electrospinning technique for wound healing applications. Rad et al. (2019) investigated the incorporation of *Calendula officinalis* extract with poly (ϵ -caprolactone), zein and gum Arabic in nanofibers by electrospinning technique aiming at skin tissue regeneration. Banerjee et al. (2021) developed a topical formulation of neem oil (*Azadirachta indica* A.Juss., Meliaceae) with liquid crystals containing water deposits, aiming its application as an anti-inflammatory, healing and anti-methicillin agent resistant to *Staphylococcus aureus*. Ali et al. (2019) also studied the development of *A. indica* extract nanofibers using the electrospinning technique with polyvinyl alcohol and chitosan for antimicrobial activity. Debone et al. (2019) developed oily-resin films of chitosan and *Copaifera langsdorffii* Desf., Fabaceae, for application in skin dressings. Alsabeelah et al. (2021) prepared nanoemulsions using *Achyrocline satureioides* extract to increase skin protection. Maghimaa and Alharbi (2020) developed silver nanoparticles of *C. longa* for antimicrobial applications and wound healing activity. Studies involving *M. chamomilla* are also reported in the literature. Dogru et al. (2017) incorporated the plant extract into silver nanoparticles in order to increase its antimicrobial activity. Bayat et al. (2019) developed chitosan and bromelain fibres for application to skin burns aiming at their healing. Abbasi et al. (2021) developed an innovative formulation of a simple ointment and incorporated silver nanoparticles and the aqueous extract of *C. limon* for skin wound healing. El Hosary et al. (2019) developed a hydrogel based on polyvinyl alcohol and *A. sativa* powder, aiming at the healing of skin wounds. Table S2 presents some examples of medicinal plants and their developed formulations for wound healing.

Patents on Herbal Formulations

The principal tendency towards producing simpler and more economically viable pharmaceutical products can be

confirmed by searching patents registered in different countries. Almost all of the inventions are owned by Asian countries, followed by Europe and America, which is not surprising, given the widespread use of plants in Asian medicine. Among the recent patents related to pharmaceutical formulations containing plant extracts and their active molecules for wound healing, a large number of documents describe the preparation of technologically simple and inexpensive formulations such as gels, creams and ointments. Most discoveries in this area associate more than one plant species in the same pharmaceutical preparation. Other patents describe the preparation of more economically viable nanosystems, which could be considered the future trend in wound repair, ensuring advantages to the medicine such as greater stability and efficacy. Furthermore, some nanofiber membranes have been patented. However, there is no guarantee that any of these patents have been licensed.

An example of patented nanofiber membrane is described by Feng et al. (2021), who developed a wound dressing from a plant extract, in the form of a fibre membrane that is formed directly on the surface of skin by using a portable or fixed electrostatic spinning device. The invention disclosed by Shin et al. (2019), describes a nanofiber for wound dressing, comprising a spirulina extract, alginate and polycaprolactone, which, according to the inventors, has a hydrophilic structure capable of retaining a large amount of water, has good skin adhesion, and can release the spirulina extract without cytotoxicity, thus being effective for the treatment of full-thickness skin wounds. Yarin et al. (2016) developed a biodegradable plant-based wound dressing composed of electrospun nanofibers formed of a blend of polymers. Table S3 describes other recent (2012 to 2022) intellectual products registered as patents in different countries.

Additional Therapies

Many molecules are employed to induce wound repair. However, some wounds, such as pressure ulcers, deep wounds, and cancerous and diabetic wounds, remain recalcitrant to all forms of treatments, or can only be slightly reduced, but remain chronic (Hassanshahi et al. 2019). In general, they are characterized by a prolonged inflammatory phase with elevated inflammatory markers, which results in high protease activity and subsequent degradation of growth factors and other positive wound healing factors; the overall consequence is impaired healing (Schultz and Cullen 2017). These wounds may be subjected to infections, which may stop or slow down wound healing, and may require the removal of the wounded limb or even cause the patient's death (Hassanshahi et al. 2019). Therefore, approaches to wound management should target different aspects of each phase simultaneously. This strategy should involve protection from infection and free radicals, modulation of inflammation, support of

cell proliferation, and acceleration of migration (Baron et al. 2020).

Conventional wound repair treatments, such as the application of different types of dressing (*e.g.*, gauze, films, hydrogels, emulsions, ointments, foams, hydrofibres), tissue-engineered skin substitutes, negative-pressure wound therapy, autologous skin grafts, and hyperbaric oxygen therapy, have been effective for most wounds. They present distinctive characteristics, are more suitable to certain wounds, and have some limitations (Han and Ceilley 2017).

The purpose of a wound dressing is to protect the wound and to assist in the promotion of the healing process. Low-adherent dressings, semipermeable films, hydrocolloids and hydrogels are the most employed wound dressings, because they restrict liquid and microbial penetration while allowing air and water vapor through it (Weller 2009). All wound dressing types were discussed in section Medicinal Plant Formulations.

Hyaluronic acid is a non-sulphated glycosaminoglycan composed by repeated disaccharide β -1,4-D-glucuronic acid and β -1,3-*N*-acetylglucosamine units. It is one of the major components of animal ECM produced by fibroblasts, synovocytes, chondrocytes, and keratinocytes. It is essential in the inflammation, granulation, and re-epithelialization wound repair phases, and its level is high in granulation tissue (Gupta et al. 2019). Many types of hyaluronic acid-based dressings have been employed over the last decade to treat various acute and chronic wounds, for example: Hyalosafe®, Hyalogran®, Hyalofill®, Hyalomatrix®, Hyiodine®, and Sorelex® (King and Sorooshian 2020). Although they present satisfactory results, recent research has investigated the association of hyaluronic acid with other biomaterials, such as collagen, polycaprolactone, poly(lactic-co-glycolic) acid, epigallocatechin-3-*O*-gallate, and growth factors such as FGF, EGF, VEGF and PDGF. These associations improve wound-healing outcomes, leading to significantly faster wound-healing rates due to fast vascularisation and wound closure; reduction of the risk of contractures, hypertrophy and keloids, optimise wound healing in deeper burn wounds (King and Sorooshian 2020). In addition to its wound healing and antimicrobial properties, the hyaluronic acid polymer yields good biocompatibility and minimal cytotoxicity within soft tissues, regardless of its concentration, when compared to other polymers, including carbomer and sodium alginate (King and Sorooshian 2020).

Tissue-engineered skin substitutes are types of wound dressing that are employed in cases of deep injuries and burns instead of surgical procedures with foreign tissues. They provide a barrier function for protection against microorganisms, reduce pain, and promote wound healing by tissue regeneration. They can be classified in several ways, based on the duration of coverage, as permanent, semi-permanent or temporary; based on anatomical structure, they

are epidermal, dermal, or dermo-epidermal (composite). They can also be cellular or acellular and, according to the type of biomaterial employed, they can be biological (autologous, allogeneic, xenogeneic) or synthetic (biodegradable, non-biodegradable). Despite their many advantages and applications, none of them can fully simulate native skin, due to the reduced vascularization, poor mechanical integrity, failure to integrate, scarring, and immune rejection of tissue-engineered skin substitutes (Vig et al. 2017).

Negative-pressure wound therapy refers to wound dressing systems that continuously or intermittently apply sub-atmospheric pressure, a differential suction (about 125 mm Hg), reducing the local pressure, creating macro- and micro-deformations at the wound surface, that stretch cells and activate molecular pathways for angiogenesis and cell division. For wounds with oedema, these devices have the ability to remove a large amount of fluid. They have been used to treat pressure sores, open abdomen wounds, sternal wounds, traumatic wounds, diabetic foot infections, second-degree burns, and skin graft recipient sites. However, negative-pressure wound therapy is contraindicated in untreated fistulas, untreated osteomyelitis, or in a wound with malignant tumour (Huang et al. 2014).

Autologous skin grafts have been part of extensive wound and burn therapy for centuries. They provide wound coverage and closure by tissue replacement, pharmacological stimulus for healing, and promote the return of proper skin function. Their classification is based on the depth of the skin harvested. When the entire epidermis and dermis are obtained, with adnexal structures, the graft is called a full-thickness skin graft. It helps prevent skin contracture and thus can improve the cosmesis of the treated area. Alternatively, grafts that contain the entire epidermis but only parts of the dermis, also with adnexal structures, are called partial-thickness or split-thickness skin grafts. Although they are effective, grafts have a high cost, require an expert surgeon, use of anaesthesia and an operating room, and creating a wound at the donor site (Herskovitz et al. 2016).

Chronic wounds are characterized for being hypoxic, and tissue repair is disrupted. The low vascular supply, chronic inflammation, bacterial infection, and decreased local metabolic oxygen production contribute to chronic hypoxia. Acute, short-term hypoxia can stimulate angiogenesis; however, chronic hypoxia impedes angiogenesis, the release of VEGF and PDGF that stimulate endothelial cell division and migration to initiate angiogenesis, bacterial killing, and lymphocyte/leukocyte migration, in addition to fibroblast division and migration to synthesize new ECM, especially collagen. In chronic wounds, the production of ROS, $O_2^{\cdot -}$, H_2O_2 and HO^{\cdot} are crucial for the upregulation of growth factors, cell signalling, and bacterial killing (Frykberg 2021). Therefore, hyperbaric oxygen therapy has been used as adjunctive to conventional wound care, especially in

chronic wounds that do not respond to the usual clinical care, because it stimulates fibroblast proliferation and angiogenesis, enhance immune function, and accelerated wound closure, and reduces the incidence of infections (Han and Ceilley 2017). Moreover, the increase of pO_2 oxygen induces to the production of ROS, performing on signalling pathways that modulate the synthesis of inflammation mediators, antioxidants and growth factors which can contribute to the healing process (Frykberg 2021).

Photo-biomodulation is an alternative technique that consists in placing light over wounds that are resistant to healing by other approaches, using light-emitting diodes (LEDs), lasers and other light sources, in the wavelength range from visual to infrared. Irradiation enhances healing and closure of these chronic wounds (*e.g.*, pressure and diabetic ulcers) by enhancing cell migration, proliferation, angiogenesis and the rate of re-epithelialization, inducing skeletal muscle healing by reducing fibrosis, and enhancing the reorganization of myofibers, stimulation of collagen, cytokines and chemokines, growth factors production around the wound periphery, reducing oedema and the number of inflammatory cells, and exhibiting antibacterial actions. It can be employed on its own or conjugated with other devices (Kuffler 2016).

In order to circumvent the limitations of conventional approaches, the use of specific stem cells with skin-regenerative has emerged as a promising approach to accelerate the wound-healing process of acute and chronic wounds. Chronic wounds are caused by depletion of stem cells and a variety of other cellular and molecular mechanisms (Han and Ceilley 2017). Many stem cells have been investigated for their capacity to differentiate into fibroblasts, keratinocytes, epithelial and endothelial cells to repair chronic wounds. Among the most important are epidermal, dermal precursor of fibroblasts, melanocyte, mesenchymal-like, adipose-derived, bone marrow-derived mesenchymal, induced pluripotent, amniotic epithelial and mesenchymal cells (Hassanshahi et al. 2019). The activities of these stem cells are strictly regulated by many growth factors, such as EGF, FGF, PDGF, TGF, VEGF, and both stem cell and the specific growth factor have been used together (Nourian Dehkordi et al. 2019). However, these cells have some limitations, which may hamper their clinical applications for wound healing. These limitations may include ethical issues, risk of tumorigenicity of particular stem cells, and risk of cell rejection by the host immune system (Hassanshahi et al. 2019).

Some approaches, such as the application of platelet-rich plasma and electrical stimulation, may also improve the rate of complete healing of chronic wounds in animal models. However, none of these approaches yield presented satisfactory results on their own, and many wounds remain recalcitrant to all techniques (Kuffler 2016; Baron et al. 2020).

Perspectives and Future Directions

The wound healing area is undergoing significant advances, because the integration of traditional knowledge with modern scientific techniques. The investigation of medicinal plants and their active molecules has already shown promising results, especially in the development of affordable and effective formulations such as gels, creams, ointments, and film membranes. However, the future of wound care is probably to prospect the most highlight with the employment of nanosystems, which offer enhanced stability and efficacy. These advanced formulations have the potential to revolutionize the treatment of chronic and hard-to-heal wounds by providing more targeted delivery of active compounds, reducing side effects, and improving patient outcomes and adherence.

Additionally, trends towards producing economically viable pharmaceutical products, particularly in regions with a rich history of herbal medicine such as Asia, suggests a growing global interest in accessible wound care solutions, as can be seen from the profile of patents registered in this area. In the future, there may be a greater focus on personalized medicine, where treatments are tailored to individual patient needs, potentially combining conventional therapies with phytotherapeutic approaches. Moreover, the association of additional technologies, such as tissue engineering and bioengineered skin substitutes, with phytotherapeutic formulations could offer synergistic effects, improving the wound healing process. It is mandatory that future researches must explore the potential of these approaches conducting rigorous clinical trials to validate their efficacy.

Conclusions

Wounds and particularly hard-to-heal wounds are important public health concern, causing pain, bleeding, disability, amputation, and may lead the host death. A vast number of plants have been empirically employed in wound treatment since ancient times. In the present day, these medicinal plants and their active molecules, especially flavonoids and proteases, have been investigated by their curative potential. Patented and scientifically developed herbal formulations, especially gels, creams, ointments, film membranes and nanosystems, are vehicles for medicinal plants, their extracts and active molecules, promoting patient adherence to the topical treatment, comfort and facilitating application to the skin and wound healing. Additional therapies were necessary to deal with hard-to-heal wounds in conjunction with topical formulations. The development of advanced and innovative herbal medicines generates better quality of life for the population, because they have good cost benefit ratio and fewer adverse effects than conventional chemical

drug therapy. So far, these phytotherapeutic formulations are promising in the current scenario based in the Green Chemistry principles.

In conclusion, the future of wound healing stands at an exciting crossroads, where traditional knowledge and modern science intersect. The traditional herbal medicines will continue to play a crucial role in wound care. The future lies in the development of more sophisticated and economically feasible nanosystems, as well as in combined therapies that can provide superior outcomes for patients with chronic and hard-to-heal wounds.

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Data Availability Data will be made available on request.

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