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Medicinal Plant Extracts and Their Use As Wound Closure Inducing Agents

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ABSTRACT Skin insult and damage start a complex healing process that involves a myriad of coordinated reactions at both the cellular and molecular level occurring simultaneously. These processes can be divided into that of cell migration and tissue remodeling of the wound. In addition, it is well known that deep wounds that derive from surgical procedures need a multidisciplinary approach to have a successful wound healing process. Recently, there has been a renowned interest in the identification of active compounds derived from ornamental, edible, and wild plants being used in the cosmetic and skin product industry. Recent reports suggest that active components of several plants such as Propolis and *Aloe vera* could be used to induce the process of wound healing and tissue regeneration and reducing therefore the time to complete wound closure. Other plant species such as *Achillea millefolium* or *Salvia officinalis* have anti-inflammatory properties and promote cellular proliferation contributing to faster tissue regeneration. It has been described that *Malva sylvestris* influences the formation of fibrosis-free granulation tissue in the skin. Recent observations suggest that *Casearia sylvestris* induces the angiogenic process. These effects have been evaluated in cell lines, different animal models, and some in randomized clinical trials. In this review we summarize the evidence of plant extracts and their active components (when known) in the acceleration of the wound closure process and tissue repair.

KEYWORDS: • ***medicinal plants*** • ***wound closure*** • ***wound healing***

INTRODUCTION

Skin is a fibroelastic membrane. It is an important organ that protects us from external insult,[1] provides the means for thermal regulation,[2] protects us from ultraviolet radiation insult, and participates in the production of vitamin D.[3] In addition, it is also a physical barrier fending off against infectious insults as part of the innate immune system.[4] Skin is the biggest organ of the human body and the most important receptor of input from the surrounding world.[5] The skin comprises two main layers as follows: the dermis and epidermis. The epidermis is the most external layer; it has no blood vessels and acts as a barrier preventing moisture loss and as a physical barrier against infection.[6]

Given the exposure of this barrier to physical, chemical, or thermal exposure it is susceptible to integrity damage.[7] In cases of integrity loss of such barrier the skin must be restored and for such tasks several processes must be undertaken to restore the skin to its normal functions.[8] This event of restoration of the skin homeostasis is known as wound healing, and its ultimate goal is to maintain the barrier integrity. It involves a series of complex interactions between different cell types, growth factors, chemokines and cytokines, enzymes, and extracellular matrix (ECM) components.[9]

The wound closure process involves several sequential steps that are triggered by vasoactive molecules that produce a domino effect of several autocrine, paracrine, and endocrine signals[10];

(a) Coagulation or hemostasis; starts by the formation of a thrombus, which protects the wound and provides a provisional ECM for the formation of new tissue,[11,12]

(b) Inflammation; mediated by several pro-inflammatory mediators such as thromboxanes, prostaglandins, and substance P, among others. This causes the release of

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cytokines and chemokines, as well as the infiltration of neutrophils and macrophages that eliminate the debris of dying cells by phagocytosis[12] of such debris and also the elimination of microorganisms from the wound,[13]

(c) Proliferation; (promoting granulation tissue formation and collagen synthesis).[14] The cells in the surrounding area of the wound start to proliferate and increase their mitotic activity due to several growth factors such as transforming growth factor-β, platelet-derived growth factor, keratinocyte growth factor, vascular endothelial growth factor, among others[15] which are being secreted at the site by macrophages and fibroblasts.[12,16] The angiogenesis and formation of new blood vessels are paramount for the tissue regeneration. In addition, the migration of fibroblasts and the remodeling of fibrin, vitronectin, and fibronectin by the migrating cells initiate the process of remodeling of the wound. After this the formation of the permanent ECM composed of type I, III, and V collagen, proteoglycans, and others is synthesized. In order for this process to happen several matrix metalloproteinases (MMPs) are secreted and contribute to the degradation of the damaged tissue.[15] At the same time there is migration of keratinocytes to the wound center in the reepithelialization process that cause the wound contraction in the edges.[16]

(d) Remodeling that determines the strength and appearance of the scarring tissue.[1] During this phase, most of the cells that were active in the proliferation phase die by apoptosis. The MMPs increase their activity given that the granulation tissue production has ceased. It is important to mention that this new tissue does not have the same characteristics as the granulation tissue; it shows a higher rigidity and exhibits a lower elasticity and flexibility due to a higher content of type I collagen and the lack of elastin.[15,16]

The successful healing of the wound when both the dermis and epidermis have been compromised depends on several intrinsic factors such as the production of reactive oxygen species (ROS),[17] lactate,[18] hypoxia inducible factors,[19] as well as of extrinsic factors such as medication,[20] emotional stress,[21] nutrition,[22] age,[10] and so on.

Throughout history, different attempts and approaches were used to cure wounds in ancient times[23] and till today it is an important matter of research worldwide. In such ancient times it was understood that the use of the correct compounds from nature would lead to wound closure.[24] Continuing with this line of reasoning a continuous expansion and a better understanding of the intrinsic and extrinsic factors that govern wound healing have been described. Despite the discovery of antimicrobial agents, antiseptics, and anti-inflammatory drugs, the wound closure process is challenging in the clinical setting of modern medicine.

Plants and natural extracts that have been used in traditional medicine are considered as potential agents for the prevention and treatment of superficial lesions of the skin, and evidence of efficacy in the clinical setting is growing rapidly. In this context this review summarizes the evidence of such plant derivatives and their use in wound healing.

PLANTS WITH POSITIVE EFFECTS IN WOUND CLOSURE

Achillea millefolium

This plant of the *Achillea* genus that belongs to the Asteraceae family is a herb and from its rhizome arises one or various stems with rare ramifications. It is characterized morphologically by the way in which the five ligules are grouped visualizing themselves as a single flower. The name of the genus is originated from the Greek mythology ''Achilles.'' The Greek hero apparently used this herbal remedy for his injured heel. Other species of *Achillea* have been used in other medicinal purposes for thousands of years.[25] *Achillea millefolium* is used in several therapeutic and pharmacologic applications: in water through the oral route as a stimulating tonic,[26] astringent,[27] spasmolytic,[28] and choleretic.[29] When used as a topical in the skin it has anti-inflammatory and healing properties.[30] It has been described that in the essential oil derived from the dried flowers and obtained by distillation it contains azulen. It has also been used in hemostasis to stop bleeding,[31] in menstrual cramps,[32] and in the treatment of gastric disorders (diarrhea) and has been demonstrated to also be useful in the gastrointestinal tract due to its antispasmodic activity.[28] Hepatic-protective effects have also been reported.[33] In 2015 Agar *et al.*[34] evaluated the antioxidant, wound closure, and cytotoxic compounds from *Achillea* and observed a strong ROS scavenging and detoxifying activity with a high binding capacity ($EC50 = 32.63 \pm 0.65$ g/mL, $P > .05$) confirming their antioxidant activity. The anti-inflammatory effects of *A. millefolium* extract are mediated by the activity of such compounds on the arachidonic acid metabolism.[35]

To evaluate the healing effect of *Achillea* at the cellular level, mice derived fibroblasts were used. When the cells were treated with the plant extract a clear proliferating effect was observed, as well as an increased production of type I collagen, which would accelerate healing. A low level of cytotoxicity was also shown.[34] Another study that used the fibroblast Hs68 cell line and the keratinocyte HaCaT cells treated with extract from *A. asiatica* (pertaining to a related species to *A. millefolium*) showed a strong anti-inflammatory activity by reducing nitric oxide production and release of prostaglandin E_2. In addition, a reduced expression of tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and cyclooxygenase-2 was observed. The authors observed that an increased wound healing promotion and increased expression of differentiation markers (b-catenin) in HaCaT cells and also in a model of wound healing in Sprague-Dawley rats were treated with *A. millefollium* extract.[36]

The effects of *Achillea* species on *in vivo* wound healing have also been evaluated in mice and rat models. A study by Akkol *et al.*[37] in 2011 showed that *Achillea* extracts compared to Madecassol (wound healing cream) indicated that

the extract had a better effect on wound healing and closure compared to the control. The data clearly showed that the treated animals had a higher activity in inducing wound healing than the reference drug.[37]

Recently, *A. millefolium* has been tested in clinical trials. In a study performed in pregnant women (first pregnancy) of Iranian descent, the wound healing and anesthetic effect were evaluated during the episiotomy recovery phase. It was shown that the extract of this plant showed a significant reduction of perianal pain, as well as redness, edema, and hematomas around the wound.[38] In this study the authors recommend the use of the extract of this plant in a commercial cream preparation for the treatment of these kinds of wounds. Until now no adverse effects have been reported on the use of *A. millefolium* extract or any of its compounds, so it can be considered as a viable option for the treatment of episiotomy wounds.

Malva sylvestris

Malva sylvestris is a plant that shows pubescent stems of 80 cm long, and in some cases even bigger species have been found. The leaves are round and hepta lobulated with small fibrils in the leaf and nerves. The plant flowers in summer and are hermaphroditic of 6 cm in diameter. The flowers are violet with nerves in a reddish color. As a fruit this plant has a capsule or nutlet containing several structures with seeds in each of these that serve as a spreading mechanism.[39]

There are many species of *M. sylvestris* (Malvaceae) being used in the popular medicine. Pre-Christian era use of the plant has been documented both for consumption and medicinal purposes.[35] Nowadays, the consumption of *M. sylvestris* has extended due to description of anticarcinogenic and anti-inflammatory properties,[40,41] antioxidant properties,[42] and skin wound healing properties.[43] Recently a study by Afshar *et al.*[44] evaluated the wound healing effect of *M. sylvestris* in a Balb/c experimentally induced skin injury model. The authors describe that those animals treated with silver sulfadiazine (SSD) and the vehicle were less able to induce wound healing than *M. sylvestris*. It induced granulation tissue and reepithelialization. In addition, the synthesis of collagen was also increased.[44]

In another *in vivo* study using a model of second-degree burn (under anesthesia), the authors compared the effect on wound healing of animals treated with *M. sylvestris* or SSD. The results clearly show that the cream with *M. sylvestris* show a shorter time for wound healing than sulfadiazine, reducing the time to complete wound healing by 10 days.[45] The data suggest the possibility of using *M. sylvestris* for clinical use for such indications, although the molecular mechanism behind such effects remains the matter of further investigation.

Salvia sp.

It is a herbal medicine with flowers resembling a blue floral array. It flowers at the end of spring and until almost the end of summer. It usually grows in plains and near farmland and not in highly humid or watery zones. The genus of *Salvia* is the biggest and most important one of the Lamiaceae family; it has around 900 species spread throughout the world, including several ornamental, edible, and medicinal species.[46] The *Salvia* has been used ancestrally as a medicine for different diseases such as reducing nocturnal sweating and to normalize menstrual and hormonal functions in women.[47] It has some hypoglycemic properties, and some one species like *S. miltiorrhiza* has been also used as a wound-healing agent.[46,48] The published data suggest that several species of *Salvia* exert various biological activities and have been used around the world as a traditional medicine approach to several diseases. Its uses include antioxidant,[49] antimicrobial,[50] anti-inflammatory,[51] pain relief,[52] antipyretic,[53] hemostatic,[52] hypoglycemiant,[54] antitumor,[55] and wound healing inducer.[56]

In a study performed by Liang *et al.*,[57] it was showed that the effects of this *S. miltiorrhiza* act as an inhibitor of MMPs. These enzymes play an important role in the wound healing process and are also involved in the inflammatory response regulation through extracellular matrix remodeling and in the migration of immune cells.[58] However, the excessive or unregulated activity of MMP contributes to the development of chronic nonhealing wounds.[59] Therefore, it is of great importance that compounds of this plant regulate the activity of MMPs. This was evaluated using rat neutrophils as a source of MMP1, 3, and 9 for such assays. It was shown that MMP-1, MMP-2, and MMP-9 are inhibited by *Salvia* extracts.[57] Therefore, there is evidence that such compounds could be used to modulate wound healing through modulation as active ingredients of formulations for wound healing or cosmetics.

Recent data support that nociception and anti-inflammatory effects of *S. officinalis* of both the aqueous and organic (butanolic) extracts of the plant show *in vivo* effects in mice. The authors used the hot plate model and also in the formalin and carrageenan model and was shown to reduce the inflammation.[60] Although several studies are still underway to fully characterize the effects of *S. officinalis* on wound healing and other potential clinical applications, the landscape looks promising for its use in wound healing and skin inflammatory diseases.

Casearia sylvestris

Casearia sylvestris is a tree belonging to the Salicaceae family. It is a small bush 4–6 m in height with elongated branches. Leaves are simple and alternated with an acuminated apex and indented margins. In the inverse the nerves are prominent. It produces small flowers in a creamy white color with a strong aroma resembling honey and uric acid. The flowers are presented in bunches or clusters. The tree flowers in July, these flowers remain until October, and the fruit is fully developed from September to December. After flowering, which can occur in the second year of life of the plant, small green and round fruit appears from 3 to 4 mm in diameter to become a fully mature red and orange fruit with three seeds in a pale brown color.[61] This plant can be found in the forests of Mexico and also in the Brazilian territory.

The hydroalcoholic extract obtained from the leaves of the plant contains a variety of chemicals among which we find: Diterpenes, triterpenes, hexanoic acid, caproic acid, etc.[62,63]

In ethnopharmacology several plants with anti-inflammatory and wound healing properties have been used. An example of such plant is *C. sylvestris*.[64] Some reports on *C. sylvestris* describe the use of such plants in the treatment of skin lesions and small ulcerations in the skin.[65] Studies of this plant have demonstrated its pharmacological, analgesic, and anti-inflammatory properties.[66,67] de Mattos *et al.* in 2007 suggested that it could be used in conditions associated with chronic pain management.[68] Recently in 2015, de Campos *et al.*,[69] evaluated the wound healing effects of this plant in a burn-wound induction model in rat and mice. The extract of the plant was compared to saline, and the authors found an important antioxidant effect, as well as antiseptic and anti-inflammatory activity. It also accelerates the wound healing process, which reduces tissue damage and improves capillary permeability.[69] These pharmacological features of the extract suggest a potential and beneficial therapeutic effect of this plant to be used in inflammatory diseases and in wound healing.

NATURAL EXTRACTS WITH WOUND HEALING ENHANCING/HEALING PROPERTIES

Propolis

Propolis is a resinous substance collected in the hind legs of *Apis mellifera* from plants, salivary enzymes, plant exudates, etc. It is composed mainly from resins (50%) vegetable oil (10%), bee wax (30%), essential oil (10%), pollen (5%), and other organic compounds.[70,71] Propolis has been used since ancient times for several diseases and applications.[72] The Egyptians used it for corpse embalming and to avoid flesh putrefaction. In addition, the Incas used it as an antipyretic agent.[72,73] Greek physicians used it as an antiseptic and for topical use in superficial wounds and in the mucosal surfaces.[74] Propolis was classified as an official drug in the pharmacopeias of the XVII century in London. In addition, due to the antibacterial activity it was widely used in the XVII and XX centuries.[75] The biological effects of propolis are, in part, mediated by flavonoid compounds terpene, caffeic acid, phenolic acid, and several ester compounds.[76]

Nowadays, propolis is a natural therapeutic commercially available in several topical presentations and is used for the treatment of infectious diseases in human and veterinary medicine. In addition, applications in cosmetology and pharmacology have been derived from this mixture of active compounds.[70] Several formulations are in the market for the treatment of the upper respiratory tract, common cold, and flu.[77] The dermatology community uses of propolis include wound healing burn treatment,[78] acne,[70] herpes infection, and genitourinary infections[79]; it has also been used for the treatment of several types of dermatological disease such as neurodermatitis.[80]

There is a wide variety of propolis depending on the vegetation of the recollection zone. One of the most studied mixtures is the red propolis of Brazil; the characteristic red color of this mixture is due to *Dalbergia ecastaphyllum* colored compounds.[81] In a study of the wound healing effects with this BRPE or Brazilian Red Propolis Extract that contained a high amount of polyphenol compounds, it was found that the animals that were treated with BRPE showed a significant reduction of the lesion area. In addition, in histological and immunohistochemical studies it was found that the number of neutrophils infiltrating the tissue was reduced compared to control animals. In the same manner it was shown that the transcription factor p-NF-κB showed a significant reduction in the animal's tissues treated with the propolis, as well as the production of pro-inflammatory cytokines. Therefore the authors provide evidence of the effects of this mixture on the wound healing process.[82]

In a study by Jacob *et al.*,[83] it was shown that the effects of propolis on fibroblast cell line could be useful in the wound healing process. In the study, the authors show that 10–100 mg/mL of the extract shows effects by increasing the migration and proliferation of these cells.[83] In another study the effect of propolis in wound healing was evaluated in the formation and metabolism of fibronectin and its effects in the formation of ECM. It was shown that there was an improvement in the formation of the granulation tissue which is a hallmark of the wound healing process.[84]

In another report of propolis on the effect of wound healing in an experimental wound model in dogs, it was reported that topically administered propolis induced a reduction of 30% in the wound area compared to control and also a reduction in the time needed for complete healing.[85] In addition, in similar models, it has been demonstrated to be safe, effective, and cheap; therefore, it could be considered as a viable option for the treatment of wound lesions.[86]

Recent studies have analyzed the effect of propolis. In 2014, Henshaw *et al.*,[87] evaluated the wound healing effect of propolis in diabetic ulcer wounds in humans. The patients received a topical administration of a product based in propolis in the wound for 6 weeks. The percentage of healed wound was photographically analyzed, and the areas of wound closure were compared to the control group that was treated with conventional antibiotics therapy. The wound area was reduced 41% compared to the control group. In addition, the authors evaluated the activity of metalloproteases 2 and 9 that were significantly elevated in the chronic wounds.[87] These observations indicate that MMP-9 correlates with wound healing and with the production of collagen. The results of this report suggest that propolis improves wound healing compared to the standard of care and, additionally, provides evidence that such treatment is well tolerated in the clinical setting. In similar settings, other studies have reported a reduction in ulcer size during the first 2 weeks of treatment compared to standard of care.[88]

The effect of propolis has also been studied in a synergic model of honey treatment in which it was shown that in an animal model the effects of propolis are potentiated by the use of honey and accelerating the wound healing process, shortening the time to complete wound closure, and increasing angiogenesis and granulation tissue formation.[89,90]

Table 1. Summary of Plants and Extracts with Wound Healing Properties

Plant	*Assay*	*Experimental model*	*Effect*	*References*
Achillea millefolium	*In vitro*	Mice fibroblasts, fibroblasts (Hs68), and human keratinocytes (HaCaT).	Acts as an anti-inflammatory agent and promotes collagen synthesis and fibroblast proliferation	36
	In vitro	Rat neutrophils (as a source of MMPs)	Inhibitor of metalloprotease activity (MMPs 1, 2, and 9). Inhibitor of interstitial collagenase activity Antioxidant effects	35
	In vivo	Wistar and Sprague-Dawley rats	Increases collagen formation and fibroblast proliferation	36,45
	Clinical	Iranian women with episiotomy wounds	Reduces itching and pain associated to the wound, as well as decrease of the wound healing time	38
	In vivo	Wistar rats and BALB/c mice	Promotes granulation tissue formation, increases collagen synthesis. Reduces fibrosis. Shortens the time to wound closure and prevents inflammation in burn wounds	30,37
Salvia officinalis	*In vivo*	Wistar rats	Anti-inflammatory effects and anti-nociceptive	60
	In vivo	Swiss white mice and Wistar rats.	Inhibits ROS production, Improves capillary permeability and angiogenesis	68
Malva sylvestris	*In vivo*	Wistar rats and BALB/c mice	Promotes granulation tissue formation, increases collagen synthesis. Reduces fibrosis. Reduces time to complete wound closure. Anti-inflammatory effects in burn wounds	45
Casearia sylvestris	*In vivo*	Swiss white mice and Wistar rats.	Inhibits ROS production and improves capillary permeability and angiogenesis	62
Propolis	*In vitro*	Human fibroblast cell line	Increases migration and proliferation of fibroblasts	83
	In vivo	Swiss white mice Dogs Pigs	Anti-inflammatory activity reduces migration and synthesis of pro-inflammatory molecules. Induces wound contraction and closure. Improves granulation tissue formation	85, 86, 89
	Clinical	Human subjects, randomized trial	Inhibits activity of metalloprotease 9. Potent antimicrobial activity. Increases wound healing. Reduces wound area compared to control.	88
Aloe vera	*In vitro*	Human fibroblast primary culture	Increases type III collagen synthesis. Induces the synthesis of hyaluronic acid. Induces granulation tissue formation in the remodeling phase	103
	In vitro and *in vivo*	Wistar rats, isolated macrophages, and macrophage cell lines	Increases wound contraction. Increases macrophage activation markers. Stimulates fibroblasts and collagen synthesis. Regulates the expression of MMP-3 and TIMP-2 in the granulation tissue.	96–100
	Clinical	Japanese women	Promotes collagen and hyaluronic acid synthesis. Improves moisturizing effect in the skin.	103

MMP, matrix metalloproteinase; ROS, reactive oxygen species; TIMP-2, tissue inhibitor of metalloproteinases 2.

Aloe vera

Aloe vera produces a mucilaginous gel in the parenchymal cells of the pulp of the plant of *A. badensis*. It is a peroneus plant pertaining to the Liliaceae family. In the traditional medicine of various indigenous populations, this plant has been used for the treatment of wounds as an adjuvant to wound healing and other skin diseases. Several reports indicate that *A. vera* has been used mainly for several conditions, such as wound healing, healing of burn wounds, immunomodulation, anti-inflammatory, and hypoglycemic (antidiabetic). *A. vera* is used commercially in several products such as sunburn cream, cosmetics, and lotions. The components of *A. vera* derived gels contain several polysaccharides, amino acids, lipids, and sterols, as well as tannins and enzymes.[91,92] These extracts are used, and the nature and properties of the different components in the mixture had not been fully characterized. Therefore it has been suggested that the individual compounds need to be isolated and fully characterized to elucidate the mechanism of action of the *A. vera* gel mixture.[93] *In vitro*, these components together with the mixture have been shown to induce the proliferation of several cell lines, and it has been fully characterized that the treatment induces a faster wound healing compared to the control[94,95]; this was shown in an animal model of wound healing in diabetic and nondiabetic Wistar rats. Some reports have also provided evidence that the effects of *A. vera* could be mediated by the effects on the immune system, particularly on the activation of macrophages.[96–99] Despite the wide use of this plant in wound healing in the popular medicine of several countries, the mechanism of action has not been fully understood.

In a study by Tabandeh *et al.*,[100] the authors evaluate the effect of polysaccharides purified from *A. vera* in Wistar rats. The animals underwent a biopsy punch–induced wound, and the isolated polysaccharides were applied topically to the wound. At later times biopsies of the healed and scarring tissue were obtained to analyze gene expression of MMP-3 and the inhibitor tissue inhibitor of metalloproteinases 2 (TIMP-2). The results suggest that the *A. vera* treated animals showed a faster wound closure and that the expression of MMP-3 was increased during the first 10–20 days postwound. The data also suggested that this improved wound healing was associated with a reduced expression of MMP-3 induced by the treatment. The authors conclude that the *A. vera* derived polysaccharides are able to regulate the expression of MMP-3 and TIMP-2 and that this event of gene expression regulation is partially responsible for the improved formation of granulation tissue and therefore for the wound healing effects and the formation of ECM proteins.[100]

A report by Khan *et al.*,[101] also suggest that the topical application of *A. vera* gel in a Wistar rat model of wound healing improved the wound closure compared to an untreated group. The authors also evaluated several markers of macrophage activation and the proliferation activity of fibroblasts and collagen synthesis.[101]

Another component of *A. vera* is the sterols: Lophenol and Cycloartenol. These have reported effects on body fat composition, alterations in glycemia, and lipid metabolism in animal models of diabetes and obesity.[102] In addition, it has been reported that *in vitro*, these sterols have effects on the mRNA profiles of primary culture fibroblasts, mainly in those associated with collagen and hyaluronic acid synthesis.[103] In the clinical setting, a double-blind randomized trial of advanced age women of Japanese descent evaluated the oral administration of an extract of *A. vera* on the depth of facial wrinkles and also in the retention of humidity in the facial and forearm skin. The results suggest that sterols derived from *A. vera* have effects on the expression of COLA31 mRNA in fibroblasts. The authors suggest that by the stimulation of hyaluronic acid synthesis in fibroblasts a higher retention of humidity and, therefore, a reduced depth of wrinkles in women is mediated by moisture retention.[103] The effects of these sterols highlight the participation of such compounds on the remodeling phase of the wound healing process. Such knowledge could be used to improve the esthetics of the wounds. Further research is needed on this matter to better understand the underlying mechanisms of *A. vera's* wound healing properties. All of the aforementioned data is summarized in Table 1.

CONCLUDING REMARKS

The wound healing process requires support in three key events. In the first place the absence of infection; second, the stimulation of repair mechanisms to promote cell migration, cell to cell adhesion, and improving tensile strength of the skin to improve elasticity and moisturizing properties of the skin. And third, the nutritional, anti-inflammatory, antiseptic, and antimicrobial effects needed for complete wound closure. As shown throughout the review, all of these processes are promoted to a certain extent by the plants or extracts that were described. Besides, the traditional use of these extracts allows for the clinical use of such plants to be further characterized in the clinical settings. The extracts and plants that are currently used have several active compounds and biomolecules that have been characterized as the ones responsible for the effects observed in wound healing and burn wounds. Further research is needed to fully characterize such effects and the active compounds responsible for such biological effects. However, nowadays, strong evidence supports the use of such plant extracts on the wound healing process. It is of great importance that individual compounds are tested to acknowledge and identify toxic or side effects and potentiate the observed beneficial effects of such mixtures of compounds. This will ultimately lead to pharmaceutical use of individual compounds with broadly characterized effects and security profiles for wound healing.

AUTHOR DISCLOSURE STATEMENT

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