v. 4, n. 5, 2024

International Journal of Biological and Natural Sciences

ALOE BARBADENSIS MILL.: A REVIEW OF ITS ETHNOMEDICINAL AND ETHNOPHARMACOLOGICAL PROPERTIES IN THE MANAGEMENT OF WOUND HEALING

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Abstract: The genus *Aloe* comprises a hundred species. Different extracts from aloe species have been widely reported in traditional medicine as possessing various biological activities. *Aloe barbadensis* Mill. (heterotypic synonym of *Aloe vera* (L.) Burm.f.) is a succulent plant popularly known as true aloe and medicinal aloe. This specie is native of the Mediterranean region, and it is now widely distributed around the world. The gel found in the leaves of the plant is commonly used to treat wounds and burns on the skin. The main chemical compounds found in *A. barbadensis* are barbaloin, aloe-emodin, and acemannan (glucomannan). Acemannan, a polysaccharide, is the main bioactive compound of *A. barbadensis* related to wound treatments. The extracts and isolated metabolites of *A. barbadensis* have exhibited mainly antimicrobial, anti-inflammatory and wound healing properties. This study summarizes the conventional use and pharmacological activities of A. barbadensis reported in the literature in the previous five years, mainly on wound healing.
Keywords: Natural product, Phytotherapy, Phytomedicine, Ethnopharmacology.

INTRODUCTION

Aloe L. is a genus belonging to the family Asphodelaceae Juss. This genus includes 587 accepted species that are native mainly to Africa, Saudi Arabia, Madagascar, and India (POWO, 2023). The species *Aloe barbadensis* Mill. is widely cultivated, mainly in Mexico and Brazil (GBIF, 2023). Confusingly, the common name of this species is also the same as that of the species *Aloe vera* (L.) Burm.f., being both traditionally known as aloe vera, babosa, burn plant, and medicinal aloe. *A. barbadensis* is usually reported as a heterotypic synonym of *A. vera*. Besides that, the National Institute of Environmental Health Sciences considered that *A. vera* specifically refers to *A. barbadensis*, which is the most common form used in aloe-based products (NIH, 2022). In this review, the authors considered both species to be the same.

In traditional medicine, all parts of *A. barbadensis* can be used. The gel is applied as an ointment to treat wounds and burns on the skin, and the green part of the leaves can be prepared as a juice or a tea for laxative purposes. Because of this, interest in the therapeutic potential of *A. barbadensis* has resulted in several studies. The compounds barbaloin, aloe-emodin, and glucomannan are the most researched medicinal components of this species. The glucomannan is highlighted as the main reason for its medicinal activity to treat skin disorders because of its ability to stimulate fibroblast growth factor receptor activity and proliferation in wounds (GYLES et al., 2020). This literature review aims to summarize the current scientific evidence on the wound healing properties of *Aloe barbadensis* published in the last few years.

MATERIAL AND METHODS

This literature review used published scientific materials collected from the PubMed®, Scopus®, and Web of Science® databases. The search was limited to articles published in English between January 2018 and December 2023. The search term basis was "*Aloe*" coupled with the subterm "wound healing". Initially, all the research publications about "*Aloe barbadensis*" or "*Aloe vera*" were included. After a first read, the following were excluded: non-pharmacological works, case reports, overviews, review articles, no pharmacological correlations to wound healing, ethnobotanical surveys, epidemiological, and demographic studies. A total of 35 studies were included in this review.

RESULTS AND DISCUSSION

Aloe barbadensis is a succulent plant that has been used for centuries for its medicinal properties. It is commonly known for its wound-healing properties, and it has been widely used in traditional medicine for treating various ailments. Over the past few years, there has been a significant increase in the number of studies investigating the efficacy of *A. barbadensis* in wound healing, which may lead to the development of new therapeutic options for patients with different types of wounds.

General trends and techniques were observed and can be highlighted in this review. The most used part of the plant is the inner gel, followed by the leaf in different extract preparations. Overall, the sample preparation methods used have reflected the diverse range of research questions and applications of *A. barbadensis* in wound healing and other biological processes. Most of the sample preparation methods included maceration, Soxhlet, and microwave-assisted extraction. Several studies extracted active compounds from *A. barbadensis* using solvents such as water, ethanol, and methanol. Some studies used animal models to investigate the effects of *A. barbadensis* on wound healing or other biological processes. In these cases, the extracts or formulations were typically administered orally or topically to the animals.

Several studies have reported various formulations, including gels, creams, ointments, and dressings of *A. barbadensis* extracts or compounds, to improve their stability or delivery. Overall, different types of formulations demonstrate the versatility of *A. barbadensis* in wound healing, and all of them have demonstrated significant potential for this purpose, indicating that this species could be a valuable natural resource for developing effective wound healing agents.

Regardless of the form of preparation, extraction, or formulation used, the studies included in this review investigated the efficacy of *A. barbadensis* in wound healing using different models, including in vitro and in vivo (animal or human) studies, showing that *A. barbadensis* has anti-inflammatory, antibacterial, and antioxidant properties that aid in wound healing.

ANTI-INFLAMMATORY ACTIVITY

The species *A. barbadensis* has been found to possess potent effects to reduce inflammation, which can contribute to promoting wound healing and preventing infection. Some studies report the investigation of the anti-inflammatory activities of different formulations of *A. barbadensis* on skin wounds in rats. Hai et al. (2019) evaluated the anti-inflammatory activity of aloe-fermented extract. Blood samples were collected from rats, and the concentration of proinflammatory factors TNF-α and IL-1β, as well as the anti-inflammatory factor IL-4, was measured using an ELISA kit. The results showed that the use of aloe-fermentation significantly reduced the production of TNF-α and IL-1β while greatly enhancing the yield of IL-4 compared to the model group, concluding that aloe-fermentation significantly accelerates burn injury healing by reducing the severity of inflammation.

Rhaman et al. (2019) investigated the anti-inflammatory activity of aloe gel on burn wounds using histological assays based on the presence of inflammatory cells and levels of angiogenesis and epithelialization. The results showed that the treatment with the formulation containing aloe gel was effective in reducing inflammation and promoting angiogenesis and epithelialization. Similarly, Tariq et al. (2019) prepared silk-derived formulations in combination with aloe gel to speed up the wound healing process in diabetic mice. Histological analysis revealed that the wounds treated with silk formulations exhibited increased growth of blood vessels and collagen fibers and significantly reduced inflammation.

Additionally, Koga et al. (2020) investigated the anti-inflammatory activity of an aloe-alginate film using histological analysis of tissue samples from rat wounds by observing collagen content, inflammatory changes, and angiogenesis. The authors found that the film stimulated angiogenesis in the proliferative phase. It also showed a significant increase in collagen type I fibers while decreasing type III fibers, promoting mature scar formation when compared to the control group. Meza-Valle et al. (2021) studied the anti-inflammatory activity of aloe-hydrogel formulated with propanediol and TEA on skin wound healing in female Wistar rats. The study observed a positive influence on inflammation, angiogenesis, and wound contraction in the group treated with the hydrogel, reducing the total healing time by 29 % and achieving complete wound closure in 15 days.

Rauwald et al. (2021) identified aloe-polyketides and determined the anti-inflammatory activity of the isolated phenolic compounds by inhibiting COX-1 and 5-LOX. In the COX-1 test, only feralolide showed 24% inhibition of MDA production, while in the 5-LOX test, all aloin-type anthranoids inhibited LTB4 production by 25-41%. Aloesin also showed 10% inhibition in the 5-LOX test, while the other tested chromones and naphthalenes did not display any anti-inflammatory activity. The study highlights the importance of low molecular phenolic polyketides in the overall anti-inflammatory activity of *Aloe*-preparations, which have been validated in clinical studies and meta-analysis for wound healing and inflammatory diseases. Overall, the studies indicate that *A. barbadensis* has anti-inflammatory properties that can be useful in treating skin wounds.

ANTIMICROBIAL ACTIVITY

Aloe barbadensis has potent antimicrobial properties, which may help to prevent infection by inhibiting the growth of bacteria and fungi, contributing to the wound healing properties. There are reports in the literature about the antimicrobial activity of aloe gel ethanol (Arbab et al., 2021) and methanol (GYLES et al., 2020) extracts with potential effects against *S. aureus* and *Salmonella* spp. Arbab et al. (2021) also found good antibacterial activity against *E. coli* and *Shigella*. A fermented extract prepared from aloe gel also evaluated with regards to its antimicrobial activity against *S. enterica* serovar Typhi, *S. enteritidis*, *S. flexneri*, *E. coli*, *L. monocytogenes*, *S. dysenteriae*, *S. aureus*, and *P. acnes*, and the results showed significant inhibition on the growth of all pathogens tested, with inhibition zone diameters ranging from 10 to 25 mm (HAI et al., 2019). Additionally, the authors found that this *Aloe*-fermentation was beneficial for the microbiota to resume their normal levels after burn injury.

Despite the well-known and significant potential of *Aloe*-gel, some authors also seek to study the antimicrobial activity of other parts of the plant against several bacterial and fungal strains. As an example, Tariq et al. (2021) obtained different fractions of aloe leaf methanol extract and observed that some fractions had significant inhibition against *P. aeruginosa* and *M. luteus*, as well as antileishmanial activity. Añibarro-Ortega et al. (2021) report the antimicrobial activity of aloesin-rich extracts obtained from aloe rind, suggesting antimicrobial effects mainly against *S. enterica* serovar Typhi, *L. monocytogenes*, and *C. albicans*.

The great potential of aloe extracts as antimicrobial agents has encouraged studies conducted using different pharmaceutical formulations and technologies, such as hydrogels, emulsions, membranes, films, and nanocomposites. The antibacterial efficacy of aloe nanocarrier in a microemulsion system (HABIBI et al.,2018), composite sponges made of fungal chitosan, tetracycline hydrochloride, and aloe extract (ANBAZHAGAN and THANGAVELU, 2018), and silver nanoparticles with aloe leaf extract (BEGUM et al., 2020) were evaluated, and all exhibited good action against *K. pneumoniae* and effects compared to ordinary antibiotics (ceftazidime and cephalothin to the nanocarrier, tetracycline hydrochloride to the sponges, and gentamicin to the nanoparticle). The microporous structure of the sponges was also highlighted to enhance the antibacterial activity by facilitating the absorption of water and the release of the antibacterial drugs through the diffusion process. Similarly, nanocomposite films of magnetic/bacterial nanocellulose (Fe_3O_4/BNC) prepared by Moniri et al. (2018) showed good antibacterial activity against *S. aureus*, *S. epidermidis*, and *P. aeruginosa* and were also effective in transferring antibiotics and other medicines to the wound, acting as an effective obstacle against any external infection.

Additionally, other drug delivery systems showed good antibacterial activity. Electrospun nanofibrous scaffolds made of poly-ε-caprolactone and aloe-extract, containing curcumin and tetracycline hydrochloride, possessed a broad spectrum of antibacterial activity against *S. aureus*, *S. epidermidis*, *P. aeruginosa*, *E. coli*, and methicillin-resistant *S. aureus* (MRSA) (EZHILARASU et al., 2019). Encapsulated *Aloe*-gel with polyvinylpyrrolidone and incorporated to iodine moieties in the form of iodine (I_2) and sodium iodide (NaI) into the polymer matrix was found to have excellent antifungal (against *C. albicans*) and promising antibacterial (against *S. pneumoniae*, *S. aureus*, *S. pyogenes*, *E. faecalis*, *B. subtilis*, *P. mirabilis*, *P. aeruginosa*, *E. coli*, and *K. pneumoniae*) activities, mainly to the *Aloe*-PVP-I_2 biomaterial, suggesting the potential to be used as disinfecting agents and against surgical site infections (EDIS and BLOUKH, 2020). Photocrosslinked silver nanoparticles-*Aloe*-silk fibroin composite hydrogel developed by Liu et al. (2021) indicated antibacterial properties against *S. aureus* and *E. coli*, highlighting the synergistic effects of silver nanoparticles and *Aloe*-gel. By using an alternate approach, an herbal toothpaste containing aloe and sodium chloride was proposed by Vajrabhaya et al. (2022), and the effect of the toothpaste on inhibiting *Porphyromonas gingivalis* planktonic and biofilm growth was compared to chlorhexidine.

Finally, other authors have correlated, compared, or combined the effects of *A. barbadensis* with those of other species. Leitgeb et al. (2021) and Kupnik et al. (2021) investigate the antimicrobial activity of fresh and lyophilized samples, ethanol extracts, and commercial products of *A. barbadensis* in comparison to *A. arborescens* against different bacterial and fungal strains. The results showed that all samples inhibited the growth of all tested microbial cells. The ethanol extracts of both *Aloe* spp. were confirmed to be good antimicrobial agents, with inhibitory properties against *B. cereus*, *E. coli*, and *P. fluorescens*. Natural juices and gels of both species were found to be more effective than commercial products, especially against *B. cereus*, *C. albicans*, and *P. aeruginosa*.

Tafi et al. (2020) investigated the antimicrobial activity of hydroethanolic extracts of *A. barbadensis* in comparison to *Salvia officinalis* against *S. iniae* (which causes streptococcosis), and the strain was sensitive to both species. Additionally, a biohybrid composed of iodine, aloe gel, salvia extract, and PVP made by Edis and Bloukh (2021) with antimicrobial properties was tested, and the results showed that the biohybrid exhibited excellent to intermediate antimicrobial activity and has the potential to be used as an antifungal agent, disinfectant, and coating material on sutures to prevent surgical site infections. Another synergistic antimicrobial effect was obtained on the cellulose acetate membranes incorporated with rosemary an aloe oils prepared by El Fawal et al. (2019) against *E. coli* and *B. subtilis*. The results showed that the membrane alone had no antimicrobial activity, but the addition of rosemary and aloe oils increased the antimicrobial activity in a dose-dependent manner. Likewise, Ogidi et al. (2021) evaluated the activity of antifungal creams (AFC) in combination with turmeric essential oil (TEO) or aloe gel (AG), and all of them revealed significant antifungal activity. The combinatorial effects of AFC with TEO or AG revealed synergistic properties. More recently, Naz et al. (2022) compared the antibacterial activity of *A. barbadensis* to that of *Adhatoda vasica* and *Amaranthus hybridus* against multi-drug-resistant *S. enterica serovar Typhi* and the other two species exhibited the highest antibacterial potential, highlighting that the *A. vasica* leaf extract exhibited the highest inhibition.

ANTIOXIDANT ACTIVITY

Aloe barbadensis has been shown to contain antioxidants, such as vitamins A, C, and E, as well as several flavonoids and phenolic compounds, which can protect cells from oxidative damage and promote tissue repair. Seven studies presented in this review investigated the antioxidant activity of *A. barbadensis* using different preparations and assays. Hai et al. (2019) investigated the antioxidative ability of a fermentation prepared from aloe gel, using various assays, including the DPPH, $O_2^{\cdot -}$, ·OH, Fe^{2+} chelation, and oxygen reduction assays. The researchers found that aloe fermentation had significantly enhanced the clearance rate of OH compared with aloe gel (76.12% vs. 68.00%, $p < 0.05$). However, there was no significant difference observed in their capabilities regarding the clearance rate of DPPH (56.12% vs. 62.83%), chelation rate of Fe^{2+} (82.00% vs. 83.50%), clearance rate of O_2^- (93.50% vs. 92.00%), and the total reducing power (0.26 µg/ml vs. 0.25 µg/ml). Therefore, the study suggested that aloe fermentation had significant antioxidant activity and could be used as an alternative to *Aloe*-gel for various applications.

Tariq et al. (2021) were intended to evaluate the in vitro antioxidant activity in different fractions of aloe leaf methanol extract, using DPPH, the ferric ion reducing antioxidant power assay (FRAP), and the phosphomolybdenum complex assay of total antioxidant capacity (TAC). Fraction 5 showed the highest DPPH, FRAP, and TAC activities. The aloesin-rich extracts obtained from aloe rind were investigated by Añibarro-Ortega et al. (2021) through the inhibition of thiobarbituric acid reactive substances (TBARS) formation and indicated their potential as antioxidant agents.

The antioxidant potential of aloe-peel-derived extracellular vesicles (A-EVs) was studied by Kim et al. (2021) using superoxide dismutase (SOD) and cellular antioxidant activity (CAA) assays. The SOD activity of A-EVs increased in a dose-dependent manner and was more than 40% at a concentration of 109 particles/mL. In the CAA assay, A-EVs were observed to reduce intracellular ROS levels in H_2O_2-treated HaCaT cells in a dose-dependent manner. The fluorescence intensity of HaCaT cells decreased markedly in the group treated with A-EVs and quercetin in a dose-dependent manner. Furthermore, A-EVs were found to upregulate the mRNA expression of Nrf_2, HO-1, CAT, and SOD genes in H_2O_2-treated HaCaT cells. These findings suggest that A-EVs can activate the antioxidant defense mechanisms and wound healing process via Nrf2 activation and could be a promising potential agent for skin regeneration.

Due to the large number of in vitro antioxidant assays available, using different methods may lead to different results, making it difficult to compare and evaluate the results available in the literature. However, studies generally suggest that *A. barbadensis* has significant antioxidant activity, and its different preparations exhibit varying antioxidant potentials. Notably, aloe fermentation and aloe-peel-derived extracellular vesicles show promising antioxidant potential, which may be attributed to the presence of bioactive compounds.

Some studies also compare and/or combine the antioxidant activity of *A. barbadensis* and other species. Leitgeb et al. (2021) investigated the antioxidant activity of fresh and lyophilized samples of *A. arborescens* and *A. barbadensis* and their ethanol extracts. The DPPH method was used to determine the antioxidant activity, with ethanol extracts of both aloes showing the highest concentration of bioactive substances and highest antioxidant activity. Similarly, Naz et al. (2022) evaluated the antioxidant activity of *A. barbadensis* extracts, along with extracts from *Adhatoda vasica* and *Amaranthus hybridus*, using a DPPH assay and suggested that these three medicinal plants contain higher concentrations of antioxidants, but *A. barbadensis* had lower antioxidant activity than the other two plants, with the maximum activity observed in the foliar parts of *A. hybridus*. However, El Fawal et al. (2019) tested the antioxidant activity of cellulose acetate (CA) membranes incorporated with rosemary and aloe oils using both ABTS and DPPH assays. The results showed that the membranes containing the extracts had excellent antioxidant ability compared to the blank, since the free radical scavenger activity of the membranes was improved by increasing the essential oil content in the mixture. This suggests that *A. barbadensis*, despite having lower antioxidant activity than some other plants, can still be incorporated into materials to improve their antioxidant properties.

Overall, the antioxidant potential of *A. barbadensis* extracts suggests that it has significant antioxidant activity, especially in its ethanol extracts, and can be used as an alternative to synthetic antioxidants. The results also propose that combining *A. barbadensis* with other natural compounds can further enhance its antioxidant activity and provide benefits for various applications.

CELL VIABILITY AND CYTOTOXICITY

The papers cited in this review are commonly involved *in vitro* experiments to evaluate the potential cytotoxic effects of different materials or extracts on cells, with a focus on wound healing applications. The experiments involve testing the biocompatibility of various materials, such as fungal chitosan-based composite sponges, electrospun nanofibrous scaffolds, and magnetic/bacterial nanocellulose nanocomposite films, as well as evaluating the cellular uptake and cytotoxicity of different extracts, such as aloesin-rich extracts. In all cases, the results showed that the aloe samples were non-toxic and had the potential for wound healing applications. The experiments were mostly under fibroblast cells, but also keratinocytes, endothelial cells, Vero cells, *Artemia salina*, and porcine liver primary cells.

Regarding the different fibroblast cell lineages, Ezhilarasu et al. (2019) and Moniri et al. (2018) both used human dermal fibroblasts (HDF) to test the ability to promote fibroblast proliferation for wound healing of nanofibrous scaffolds and nanocomposite films, respectively. The biocompatibility of the scaffolds was evaluated through MTS assay, CMFDA staining, Sirius red staining, and F-actin staining, and the nanocomposites were evaluated using MTT assay. Both matrices were found to be non-toxic and biocompatible, with excellent wound healing efficiency. Other fibroblast cells were used by Vajrabhaya et al. (2022), Liu et al. (2021), and Shafaie et al. (2020). The first authors performed the cytotoxicity assay using human gingival fibroblast (HGF) cells and the MTT assay, and the results showed that the herbal toothpaste is non-toxic. The second study used L929 mouse fibroblast cells and a CCK-8 assay, and the results showed that the hydrogel did not exhibit cytotoxicity towards the L929 cells. Shafaie et al. (2020) assessed the cell viability using the MTT assay and both fibroblast and endothelial cells. The results showed that aloe gel had no toxicity on both cells, fibroblasts had a higher proliferation rate, endothelial cells did not proliferate in the first 24 h, and its optical density significantly decreased after 48 h. Kim et al. (2021) investigated the cytotoxicity of aloe peel-derived extracellular vesicles (AEV) using the WST-1 assay. In the in vitro cell viability assay, HaCaT cells were used, and the results showed that cell viability was maintained above 95% at all doses of AEV.

Rahman et al. (2019) and Tariq et al. (2019) tested by Brine Shrimp Lethality assay the cytotoxicity of aloe gel-human amniotic membrane and aloe-leaf methanol extract fractions, respectively, and the results showed that for the first one, the concentrations of 250 mg/mL did not affect the viability, and for the second one, the fractions with low LD_{50} values are more active and have high cytotoxic potential, highlighting the fraction 6, which depicted the highest cytotoxicity with an LD_{50} of 530 mg/mL (TARIQ et al., 2019). The Vero cells (an African green monkey kidney cell line) and the MTT assay were employed to analyze the potential cytotoxic effects of the fungal chitosan-based composite sponges loaded with aloe extract. The results showed that the sponges did not exhibit any cytotoxic effects and increased the proliferation of cell numbers. In addition, no changes were observed in the morphology of the Vero cells after treatment (ANBAZHAGAN et al., 2018). Porcine liver primary cells (PLP2) and sulforhodamine B assays were used to evaluate the potential of aloesin-rich extracts, showing no toxicity, indicating that the extracts are safe for non-tumor primary cells (AÑIBARRO-ORTEGA et al., 2021).

WOUND HEALING

Regarding the evaluation of wound healing in the context of *A. barbadensis* usage, various techniques and methods have been applied in the literature, including in vitro and/or in vivo approaches (primarily using rat and human models). The assessment involves direct observation of treated wounds and monitoring of any changes in the healing process, such as diminished redness and inflammation, as well as improved overall appearance. Measuring tools are utilized to compare wound dimensions, determining if the treatment reduces the wound size or accelerates the closure of the wound edges. Furthermore, the formation of healthy granulation tissue is evaluated by analyzing cellular components, inflammation levels, and the presence of growth factors known to facilitate accelerated wound healing. Another approach involves examining wound fluid from treated wounds to gain insights into the presence of beneficial compounds, such as antioxidants or anti-inflammatory agents, that may contribute to the healing process. Additionally, gathering feedback from patients who have undergone the treatment for their wounds can provide valuable insights into their perceived pain levels, wound discomfort, and overall satisfaction with the healing process.

The *in vitro* evaluation focused primarily on the scratch assay. Various cell lineages were employed, with fibroblasts being the primary and predominant choice. Shafaie et al. (2020) compared the potential of aloe gel in the migration of fibroblasts and endothelial cells and observed a higher proliferative effect on fibroblasts than endothelial cells, with the induction on the migration of fibroblasts toward the scratch area and the number of migrated fibroblasts significantly higher in the treated group than controls. Moniri et al. (2018) also evaluated their aloe nanocomposite films on fibroblast cells, and the results showed that they enhanced the migration and wound closure of the cells, indicating their potential as a wound dressing for cutaneous wounds. Rahman et al. (2019) and Kim et al. (2021) studies compared the potential of their matrices (Aloe-gel membrane and Aloe-peels extracellular vesicles, respectively) using fibroblasts and human keratinocytes (HaCaT) cells. Both studies showed that the treatments promoted the migration of both cells, but the first study observed that HaCaT cells migrated faster when compared to fibroblasts, and the second study observed a closure rate higher for fibroblasts than keratinocytes. Additionally, Ezhilarasu et al. (2019) tested the ability of its nanofibrous scaffolds to promote fibroblast proliferation for wound healing using fibroblasts through other methods, such as the MTS assay, CMFDA staining, Sirius red staining, and F-actin staining. The results demonstrated that its nanofibrous scaffolds were non-toxic and had the potential for wound healing applications.

The *in vivo* evaluation of aloe samples was tested primarily in rat models. Tariq et al. (2019) investigated the wound healing effects of silk sericin and silk fibroin individually and in combination with aloe gel in diabetic mice, and the combination of 5% silk fibroin and 5% aloe gel was the most biocompatible in terms of the reduction of the healing time and the increase of the wound contraction compared to the control group. Kaewsrisung et al. (2021) also investigated the potential of its treatment in diabetic mice, testing an oral treatment on the improvement of wound healing and inhibition of matrix metalloproteinases (MMPs). The results showed that oral aloe had a glucose-lowering effect in diabetic mice and led to a higher wound closure rate, blood flow, capillary vascularity, and lower MMP-2 and MMP-9 expressions compared to the diabetic group. Koga et al. (2020) found that aloe-alginate film enhanced the healing process of incisional skin wounds. The percentage of wound contraction was 80.6%. Ashkani-Esfahani et al. (2019) evaluated and compared the effectiveness of *Plantago major* and aloe gel treatments. The results showed that the treatment with the mixture of both species improved wound healing by enhancing fibroblast proliferation, collagen bundle synthesis, and re-vascularization in skin injuries.

Aloe hydrogel formulations were produced and tested in vivo on rat models by Meza-Valle et al. (2021) and Liu et al. (2021). The Meza-Valle et al. (2021) assay showed that the hydrogel reduced the total healing time by 29%, resulting in complete wound closure in 15 days. The hydrogel promoted wound contraction, reduced inflammation, and angiogenesis. Biopsies showed improved quality of the healing tissue compared to the control group. The mathematical estimation of the complete closure of the wound represents a 75% reduction in the healing time. The healing-promoting ability of the aloe-photocrosslinked hydrogel prepared by Liu et al. (2021) was found to be stronger than the single-modifier groups, with a healing rate of 97.02% on day 21, higher than the commercial formulas. The histological and protein expression results showed that the hydrogel had a greater effect on the pro-healing regenerative phenotype of M2 macrophages at the early stage, reconstructing the blood vessel networks and inhibiting the formation of scars. The results suggest that the hydrogel has great potential for improving wound healing in clinical treatment.

Alternatively, Hai et al. (2019) used an animal model of burn injury. The results showed that aloe fertilization significantly accelerated the healing of burn injuries. Histological analysis revealed that aloe fermentation produced more eosinophils and fibroblasts and less vessel proliferation compared with the model group, indicating that it had a better effect on accelerating the wound to normal levels.

Studies has demonstrated that *A barbadensis* gel has proven to be effective in the treatment of various types of wounds in humans, including chronic wounds, skin ulcers, burn wounds, and excisional wounds. Hekmatpou et al. (2018) report a randomized, triple-blind clinical trial that investigated the effect of aloe gel on the prevention of pressure ulcers in hospitalized patients. The results showed that the incidence of pressure ulcers was significantly lower in the intervention group that received aloe gel compared to the control group ($P = 0.047$). The authors concluded that applying aloe gel could prevent the occurrence of pressure ulcers in hospitalized patients by preventing a rise in temperature, non-blanchable redness, swelling, and pain of the skin in regions at risk of pressure ulcer development.

A recent systematic review conducted by Idrus et al. (2023) has found promising evidence suggesting that aloe gel could serve as a viable and economical option for the treatment of chronic wounds. Another systematic review published by Hekmatpou et al. (2019) also emphasized the potential of aloe gel in preventing skin ulcers and treating different types of skin wounds. These include burns, post-operative wounds, nipple fissures, genital herpes virus, psoriasis, and chronic wounds. Also, according to a study conducted by Visuthikosol et al. (1995) with 27 patients with partial thickness burn wounds, aloe gel has been found to be more effective than vaseline gauze in the healing process.

In summary, further research is needed to fully comprehend the mechanisms and potential applications of aloe gel in clinical practice, despite the progress made in its clinical evaluation.

OTHER PHARCOLOGICAL ACTIVITIES

Some other pharmacological assays correlated to the wound healing purpose were accomplished in aloe samples. Regarding the bioactive compounds of *A. barbadensis*, docking analysis performed by Tariq et al. (2021) showed that this species contains anthraquinones, anthrones, chromones, and polysaccharides responsible for the synergistic cytotoxic, antileishmanial, antibacterial, and antioxidant potential of this plant.

The enzymatic activity of *A. arborescens* and *A. barbadensis* was investigated and compared by Leitgeb et al. (2021). The study focused on the activity of various industrially important enzymes, including α-amylase, cellulase, lipase, peroxidase, protease, and transglutaminase. Results showed that *A. arborescens* had the highest α-amylase and cellulase activities. Lipase, protease, and peroxidase activities were highly detected in *A. barbadensis*. The presence of the enzyme transglutaminase, which is important in wound healing, was detected in samples of both *Aloe* spp.

Moniri et al. (2018) and Shafaie et al. (2020) evaluated the gene expression of their aloe samples by real-time polymerase chain reaction (RT-PCR). The first study involved the expression of the genes TGF-β1, MMP2, MMP9, CTNNB1, Wnt4, hsa-miR-29b-3p, and hsa-miR-29-c-3p, determined after treating

International Journal of Biological and Natural Sciences ISSN 2764-1813 DOI https://doi.org/10.22533/at.ed.813452413069

HDF cells with the nanocomposites. This study also involved a bioinformatic analysis, which identified pivotal genes and miRNAs involved in wound healing. The authors identified the proposed genes, as well as collagens, which have a significant role in wound healing, and also provided insights into the molecular mechanisms involved in wound healing, highlighting the potential of the nanocomposites for promoting wound healing. The second study was used to evaluate the gene expression of integrins α1 and β1 and PECAM-1 in fibroblasts and endothelial cells, and the results showed that the aloe gel increased the expression in both cell types, the fold change was significantly higher in fibroblasts, and the protein level of PECAM-1 showed no change in both cells upon aloe gel treatment. The study concluded that aloe gel induced angiogenic and cell adhesion properties in fibroblasts more than endothelial cells, suggesting the main role of fibroblasts rather than endothelial cells in wound healing by aloe gel administration.

Furthermore, to analyze the irritability and applicability of the aloe gel, an in vivo study and a rat model for artificial burn induction, re-epithelialization, and wound contraction assays were performed by Rahman et al. (2019). The results showed that the gel did not induce any edema or erythema, indicating the safety of gels for topical application. The group treated with aloe gel showed the fastest healing rate with more scar tissue and also showed the shortest re-epithelialization period.

Finally, the study by Tafi et al. (2020) investigated and compared the therapeutic effects of aloe and salvia hydroethanolic extracts against *Streptococcus iniae* in rainbow trout. At the end of the study, aloe showed the best therapeutic effect and significantly reduced the mortality rate of infected fish, also demonstrating the best performance in moderating histopathological lesions in the gills and livers of the treated fish compared to other groups. The results suggest that aloe could be useful for treating streptococcosis caused by *S. iniae* and reducing histopathological lesions in rainbow trout.

FUTURE PERSPECTIVES AND CONCLUSIONS

Based on the findings, future perspectives for *A. barbadensis* in wound healing research include further investigation into the underlying mechanisms of action, including the potential role of specific active compounds and their interactions with various signaling pathways. Additionally, there is a need for more standardized protocols for preparing the extracts and formulations to ensure consistent results across different studies. Moreover, more clinical trials are needed to evaluate the efficacy and safety of the species in wound healing, particularly in comparison to conventional treatments. Finally, there is potential for the development of novel aloe-based wound dressings and delivery systems that can improve the bioavailability and targeted delivery of active compounds to wound sites.

In conclusion, the scientific evidence supports the traditional use of *A. barbadensis* for wound healing. The species has been shown to have anti-inflammatory, antibacterial, and antioxidant properties, as well as the ability to stimulate collagen and fibroblast production, improve angiogenesis, and re-epithelialization of wounds. Further studies are needed to fully understand the mechanisms underlying the wound healing properties of *A. barbadensis* and to optimize its use in wound care.

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