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An overview of Aloe vera impact on the healing process of Diabetic Foot Ulcer

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ABSTRACT

Introduction and aim Diabetic foot ulcer (DFU) is a chronic condition that affects an increasing number of people each year^[1]. Healing the ulceration requires cooperation between patients, specialists and scientists in order to achieve satisfactory results. Treating this type of wound is not only a therapeutic challenge^[1,2,3,4,5,6], but also an economic one, which is why so much scientific research has already been made on this phenomenon^[2,3]. Still scientists continue their quest for new cost-effective alternatives to current therapeutic options that would be consistent with contemporary knowledge and available engineering capabilities in pursuance of creating techniques and new dressings that will accelerate the healing of DFUs^[2,3,7,8]. Factors such as stress, obesity, certain medications, and chronic diseases appear to negatively affect the process of repair^[1,9,10,4,6,11]. Studies prove that aloe vera gel due to its healing properties, can be considered as a potential dressing that will expedite the mending process of diabetic foot ulceration^[12,13,14].

In this paper, we performed a literature review of the applicability of aloe vera in the healing process of DFUs.

Materials and methods Searching the available literature, including randomized clinical trials and systematic reviews, we drew on databases focusing on the effects of treatment for diabetic foot ulceration using Aloe vera.

Conclusion: The current scientific research on the use of Aloe vera gel in diabetic foot ulcer treatment indicates that this method is safe, effective and inexpensive^[2,3]. However the difficulty of treatment and the increasing prevalence of this type of wound pose a challenge to finding new solutions and exploring mechanisms in which aloe vera can have a possible role in the wound healing process. Nevertheless, this paper presents a promising impact of Aloe vera gel applicability in the healing process of diabetic foot ulcer.

Keywords: diabetic foot ulcer, diabetic wounds, diabetic foot ulcer classification, Aloe vera, Aloe vera hydrogel, DFU treatment

Introduction

Diabetic foot ulcer is a type of wound that millions of people worldwide suffer from. It is associated with about 30% mortality in terms of five-year survival rate^[1]. This disease entity is characterized by complex pathophysiology, which implies the difficulty of treating this type of injury^[15,16,17]. There has been a need to classify the severity of DFU in order to assess the effectiveness of the therapies undertaken, the most prevalent of those being the Wagner scale, PEDIS and the University of Texas scale^[18,19,20,21]. Neuropathy, peripheral arterial disease and hyperglycemia are factors that negatively affect the treatment process of diabetic foot ulceration, which remains the greatest challenge^[1,22,23,19]. Treatment of this condition is complex and requires compatible methods to ensure optimal healing. The medicinal qualities of Aloe vera have been appreciated since biblical times^[11]. The plant has been used to treat various types of wounds, burns, even ones difficult to treat^[24,25,27]. The leaves of the plant containing medicinal substances have been studied^[12,13,14], unequivocally providing evidence of the effectiveness and validity of the use of Aloe vera in the treatment of diabetic foot ulceration.

Aim

The purpose of this systematic review is to purvey current developments of using Aloe vera gel to the healing process of diabetic foot ulcer.

Material and methods

Cochrane Database of Systematic Review, Pubmed, Google Scholar and ResearchGate databases were searched for the phrases: "diabetic foot ulcer", "diabetic wounds", "diabetic foot ulcer classification", "Aloe vera", "Aloe vera hydrogel", "DFU treatment" in English-language literature. We have selected articles from those published between 2003-2023.

Diabetic foot ulcer

Diabetic Foot Ulcers (DFUs) are a complication of diabetes that can lead to serious consequences such as infections, hospitalizations, limb amputations, or even death^[9,3]. Many risk factors contribute to wounds that eventually develop into ulcerations^[16]. Treating DFU is expensive^[3,6], and we currently face a shortage of new and effective treatments in developing countries ^[3]. Available data suggest that recently in some countries , the amputation rate has increased by 50%. That is why it is so important to prevent wounds from occurring and to use care based on the experience of many specialists following the current medical knowledge ^[28].

Epidemiology

According to estimates by the International Diabetes Foundation, about 40 million to 60 million people worldwide are stricken with Diabetic Foot Ulcer ^[28].

Each year nearly 1,8 million people around the world struggle with the treatment of diabetic foot ulcers. In a group of patients diagnosed with diabetes, lower-extremity amputations were preceded by the presence of an ulcer in 80% of cases and were an important factor in the increased risk of death^[1].

Pathophysiology of diabetic foot ulcer

Neuropathy, occlusive vascular disease and lower extremity trauma with subsequent infection are factors responsible for the development of diabetic foot ulceration. The ulcerations may be the result of repeated minor trauma caused, for example, by ill-fitting footwear ^[15].

The worsening of trauma sensation in diabetic patients is due to the loss of protective pain and temperature sensation contributing to the formation of blisters and abrasions ^[10].

Loss of myelinated fibers is the cause of motor neuropathy, which is responsible for foot deformity(e.g.hammer-toe^[15], claw toe ^[10],pes cavus, Charcot arthropathy,hallux valgus ^[17], muscle atrophy and abnormal gait. These changes are predisposing factors in the formation of diabetic foot ulcers.

Diabetic foot wounds (a) and factors associated with their occurrence(b).

Classification systems of diabetic foot ulcer - PEDIS, Wagner scale, University of Texas.

PEDIS, Wagner scale and University of Texas systems are the most widely used classification systems for diabetic foot ulcers [18,29]. Those scales relate to the correlation between wound severity and the potential risk of limb amputation [18].

PEDIS system

Developed by the International Working Group of the Diabetic Foot (IWGDF)^[20,30], the PEDIS scale is an acronym for the following components: perfusion, extent, depth, infection and sensation [20].

The PEDIS classification systematizes ulcers according to 4 grades. Grade 1 means that peripheral arterial disease (PAD) is absent, there are no open lesions on the skin, no infection, and sensation is preserved. PAD, without critical limb ischemia (CLI), involvement of less than 1cm² of the skin surface, superficial wound with loss of normal sensation in the limb is grade 2. The occurrence of CLI, wound occupying 1-3cm², depth reaching fascia, tendon and muscle, and the presence of

abscess or septic arthritis is assigned to grade 3. The grade indicating the highest severity i.e. grade 4 is given when the area exceeds 3cm², the wound reaches the depth of bone or joints, SIRS will occur as a result of infection [21].

Meggitt-Wagner system

In 1976, Maggit proposed a five-stage classification system, which Wagner disseminated three years later [19,31].

The Wagner classification distinguishes six grades. Grade 0 is given when there are pre- or postulcerative sites. Grade 1 applies to superficial ulcers. Penetration of the ulceration into the joint capsule or tendons classifies the wound to grade 2. Grade 3 is given to wounds that involve deeper tissue layers. Grade 4 refers to the appearance of forefoot necrosis. Grade 5 necrosis affects more than 2/3 of the foot [20,32].

University of Texas

The University of Texas classification divides diabetic foot ulcers not only by 4 grades, but also by 4 stages. Grade 0 refers to completely healed pre- or postulcerative skin lesions. Superficial wounds that do not penetrate the tendon, bone, or joint capsule are classified as grade 1. Grade 2 are ulcers that occupy the tendon or joint capsule. Grade 3 involves lesions involving joints and bones. Stage A (no infection and ischemia), stage B(infection present, no ischemia), stage C(no infection, ischemia present), stage D(occurrence of both: infection and ischemia) [20,32].

The Bates-Jensen Wound Assessment Tool (BWAT)

The Bates-Jensen Wound Assessment Tool (BWAT) is a useful tool for describing wound progression and distinguishes 13 aspects that can be divided into objective and subjective. Objective characteristics include: (1) wound size, (2) depth ,(3) edges, (4) undermining. All of them are rated from 0 to 5. Subjectively rated features include: (5) type of necrotic tissue , (6) amount of necrotic tissue, (7) type of exudate, (8) amount of exudate, (9) tissue discoloration in the wound area, (10) tissue edema, (11) tissue induration, (12) granulation tissue, (13)epithelialization.The range of scores is between 9-65[33].

Difficulties in the healing process of diabetic foot ulcers

Hyperglycemia, high-oxidative stress, peripheral neuropathy, microvascular abnormalities, chronic inflammatory processes, and infections actually contribute to the complexity of the pathology of this disease entity^[23,5].

Principles of care and goals of treatment

The pillar of ulcer treatment is a triad of principles, which include patient education, sharp wound debridement, and off-loading foot pressure. The treatment process should include: surgical wound debridement and care of damaged skin, dressings to maintain a moist environment, assessment of limb vascular capacity, limiting the development of potential infection, and maintenance of normal glycemic values^[4]. Studies have shown that multidisciplinary care of DFU patients has helped reduce limb amputations^[22]. The main purpose of treatment is to heal the tissues and preserve their function and provide weight-bearing with efficient movement^[15].

The medical value of aloe vera

Aloe vera is a plant whose name is derived from the Arabic word 'Alloeh' meaning something bitter and genial^[25]. The medicinal qualities of this plant have been valued since antiquity^[25,13,11].

The gelatinous consistency substance extracted from the uneven-edged leaves^[25] of this plant contains many bioactive compounds such as polysaccharides, sugars, minerals, proteins, lipids and phenolic compounds. Considered one of the most essential components of the gel, acemannan has many applications, particularly in metabolic, circulatory, or wound healing disorders^[26,13].

Preparation of Aloe vera Hydrogels

The gel extracted from aloe vera has anti-inflammatory and antimicrobial properties, which affect tissue regeneration and wound healing. The gel extracted from the sharp-edged leaves forms the base of the hydrogel^[25,13]. The process is

based on removing the yellowish outer layers of latex, due to its potential irritant properties, and obtaining a colorless gel previously washed with distilled water or ethanol to remove impurities. Hydrogel formulations mostly use a concentration of 1-10% (weight/volume). Taking into account the following parameters: gelation time, biocompatibility and stability of the resulting product, a hydrogel is formed by combining the gel with a hydrophilic polymer (crosslinking agent). The final step is washing with distilled water to get rid of the remaining agent that did not react with the gel and other compounds that were formed during the production process. In order to ensure proper moisture content, the reaction product should be stored in a place with a sufficiently low temperature^[13].

Aloe vera plant(a) and leaf structure(b)

Aloe vera in the wounds healing process

Wound healing is a complex process based on multiple interacting mechanisms, involving many cellular factors including inflammatory mediators, TGF- α , VEGF, TGF- β , PDGF, KGF, FGF, IGF-1, IFN and many others^[24,34]. There are four main phases of healing: (1) homeostasis, (2) inflammation, (3) proliferation process, (4) tissue remodeling^[35]. In the first stage, blood coagulation occurs, which involves the

feeding of fluid blood. Already at the time of injury, the inflammation process begins and lasts about four days. The inflammatory period overlaps with the proliferation phase, as it begins as early as the third day after the epithelial continuity is damaged. The final stage is the process of tissue remodeling. It is during this phase that granulation tissue is formed. This final stage can last up to several months^[34].

Aloe vera, due to its anti-inflammatory and healing properties, has found applications in wound and burn treatment, and the effectiveness of Aloe vera in this process is proven by many scientific studies^[24,23,5,7,27].

One such piece of evidence is a 2016 study on the effects of Aloe vera gel and Cape aloe extract on human keratinocytes in wound healing. Japanese laboratories extracted these substances from plant leaves using hot water. The resulting product was then evaporated under sufficiently low pressure, and finally lyophilized. Histological tissue methods were used to measure and evaluate the effects. The study proved that in the case of wound treatment with Aloe vera, there was a faster migration of keratinocytes in effect inducing the wound healing process^[27].

The use of Aloe vera in the treatment of diabetic foot ulceration.

In a 2014 study conducted on Wistar rats, Aloe vera gel was shown to have alleviating properties and positive effects on the healing process of diabetic foot ulceration. The study looked at the effect of using Aloe vera gel on the effectiveness of DFU treatment. The study used a division into four groups:(1)control group, (2)untreated rats, (3) rats treated with an ethanol extract extracted from Aloe vera, (4) rats whose diabetic foot ulcers were treated with Aloe vera gel. On the fourth day of the research experiment, only those rats whose blood glucose levels were higher than 300 mg/dl were selected. In the groups where Aloe vera gel and ethanol extract were used, a faster reduction in the extent of ulceration was observed compared to rats not treated with these substances. Presumably, Aloe vera gel on the healing process of ulceration by

maintaining a moist environment, influencing epithelial cells, accelerating collagen maturation and reducing inflammatory processes within wounds^[7].

The 2021 study examined the use of a combination of: silkworm fibrin and aloe vera gel. Using biomedical engineering techniques, a film of extracted fibroin was obtained and treated with distilled water and lactic acid. A grade 1 ulcer classified according to the Wagner scale was treated with the film, and the results were observed for four weeks. Wound extent measurements were documented using digital photography.

Analysis of the data showed the reduction of the wound and the effectiveness of the tested ulcer treatment method, i.e. a positive effect on the healing process of the diabetic foot ulcer. In addition, the occurrence of allergic reactions was not observed, which is an additional important aspect ^[8].

Randomized clinical trials conducted in 2019 looked at demonstrating the efficacy of a method using aloe vera gel in the healing process of diabetic foot ulcers. The study involved 40 patients randomly placed in 2 groups:(1) a study group containing patients who received the aloe vera gel preparation, and (2) a control group where a placebo was used. The aloe vera gel was applied twice a day and the result of its effect was observed and studied for four weeks. Effects were measured by means of a checklist and photographs. In the group where aloe vera gel was applied, a reduction in wound area was observed. Aloe vera gel was shown to have a potentially beneficial effect on the healing process of DFUs^[2].

The subsequent randomized double-blind clinical trial conducted in 2023 also sought to prove the validity of the theory of using Aloe vera gel in DFU healing. A randomized allocation of 66 patients with DFU was performed. The first group is the research group and the second group is the control group. In both groups, the technique of washing the wounds with saline was applied and the wounds were dressed using sterile gauze. In the research group, aloe vera gel was applied under the dressing after washing the wound. Over a period of three weeks, the effect of the gel on the healing process was studied using The Bates-Jensen Wound Assessment Tool. The study demonstrated the effectiveness of the gel application in the healing process by observing a reduction in wounds ^[3].

Conclusions:

Scientists are attempting to understand the nature of the mechanisms of diabetic foot ulcer formation and to match appropriate therapies and dressings selected for this disease entity^[22,23]. A number of therapeutic methods have been developed so far, however, the prevalence of ulceration, the complex mechanisms of healing^[34,35], the factors that impede the process and the cost associated with therapy, present a challenge to the modern world of scientists. This has prompted researchers to create methods based on the use of plants with healing properties that include Aloe vera^[24,25,27]. Studies provide us with scientific evidence of the effectiveness of using this plant in the treatment of diabetic foot ulceration. A beneficial effect has been shown with the use of Aloe vera in the healing process of this type of wound, and this we were successful in compiling in this review ^[2,3,7,8].

Supplementary materials

Diabetic foot wounds (a) and factors associated with their occurrence(b).

Aloe vera plant(a) and leaf structure(b).

Author's contribution

Conceptualization, AK, MP, ŁC ; methodology,AK, GK, JF; software, GK, MP, ŁC; check, MP, JF, ŁC; formal analysis, ŁC, MP; investigation,GK, MP; resources,AK, GK, JF, data curation, AK, GK, JF, ŁC; writing - rough preparation, AK, ŁC, JF; writing - review and editing,AK, GK, JF, ŁC; visualization, AK, MP; supervision, AK;

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