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An Overview : On the Potential use Medicinal Plants in Diabetic Foot Ulcer

Jasbir Upadhyay*

Department of Pharmaceutical Sciences, Chitkara University, Chandigarh, India

Review Article

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***For Correspondence :** Jasbir Upadhyay, Department of Pharmaceutical Sciences, Chitkara University, Chandigarh, India;

Email: Jasbirupadhyay@gmail.com

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ABSTRACT

The complications of diabetes became a heavy burden to the patient as well as physician. Among the various complications, Diabetic Foot Ulcer (DFU) is important since the major deaths in diabetes are due to DFU, which arises as a consequence of complicated and multi-factorial pathologies. The treatments using a single strategy may unlikely less effective and also the overall costs of these therapies are high. From long since, many commonly used herbs and spices are claimed to have wound healing effects with various mechanisms. Hence their application in the treatment of DFU may not only synergize the diabetic wound healing but also reduce the overall cost. This review discusses the possible use of herbs in treating DFUs with their mechanisms.

Keywords: Diabetes Mellitus; Diabetic foot ulcer; Diabetic neuropathy; Herbal; Multi factorial pathologies

ABBREVIATIONS

DM: Diabetes Mellitus; DFU: Diabetics Foot Ulcer; ECM: Extra Cellular Matrix; ROS: Reactive Oxygen Species; SDF: Stromal Cell Derived; PKB: Protein Kinase B; MRSA: Methicillin Resistant *S. aureus*; PAD: Peripheral Arterial Disease; TNF: Tumour Necrosis Factor; IL: Interleukin; MMP: Matrix Metallic Proteinase

INTRODUCTION

About 10% of 250000 plant species have been scientifically studied and found to have potential uses in healthcare. Some of the plant derived compounds such as vinblastine, vincristine, taxol, and digoxin have been synthesized because of the high demand and limited supply from natural resources. Recent development of traditional medicines has led to the extensive use of natural products and their derivatives which contribute to more than half of the total medicines consumed worldwide.

Peripheral neuropathy, peripheral arterial disease, poor glucose control, poor footwear, underlying infection and duration of diabetes, cigarette smoking, and diabetic nephropathy are recognized risk factors for foot ulceration. Patients with peripheral neuropathy are at risk of developing neuropathic ulcers [1].

DFU can lead to critical complications in the absence of proper care to the wounded area. The healing process of foot ulcers is complex and is also interrupted by local factors such as moisture, infection, and the dressing method along with systemic factors such as age and nutritional status. Effective management of DFU starts with physical examination and selection of an appropriate wound care intervention. The focus is on achieving the goal of rapid and complete wound healing. In the holistic approach of wound management, three main areas addressed are tissue loss, ischemia, and infection.

In addition, the debridement of the wound is done regularly to keep it free of nonviable tissue. Suitable dressings are used to reduce the risk of infection, improve outcomes by controlling bacteria in the wound, and provide an optimal healing environment [2].

Wound irrigation is one of the essential components of wound management. It is the single greatest intervention in wound care that can reduce the risk of infection. The goal of wound irrigation is to remove foreign material, decrease bacterial contamination of the wound, and to remove cellular debris or exudate from the surface of the wound.

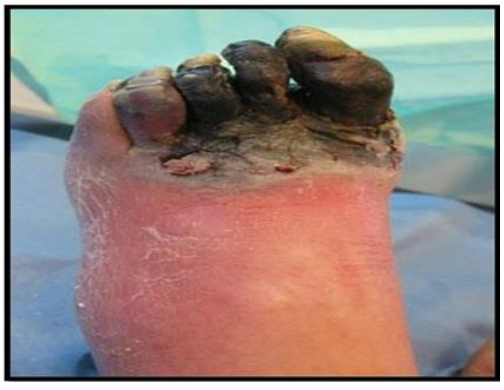
Irrigation stimulates neovascularization and healthy cell proliferation. Common irrigation solutions used for wound irrigation are normal saline, sterile water, or potable water when normal saline or sterile water is not available. Some compounds such as hydrogen peroxide, eusol, and collagenase ointment are also used for foot ulcer.

LITERATURE REVIEW

A process with four typical stages: Haemostasis, inflammation, proliferation, and remodelling involving many cell types, cytokines, and Extra Cellular Matrix (ECM), and macrophages generate more Reactive Oxygen Species (ROS) to defend against foreign pathogens. Excessive ROS can damage normal cells and tissues, cause nutritional deficiencies, and impair angiogenesis, hypoxia, and neuropathy, ultimately leading to persistent inflammation and long term persistence. Non-healing chronic wounds [3].

The use of wound dressings is the most direct and convenient way to prevent microbial infection of wounds and has been used in wound care for a very long time (Figure 1).

Figure 1. Diabetic foot ulcer.



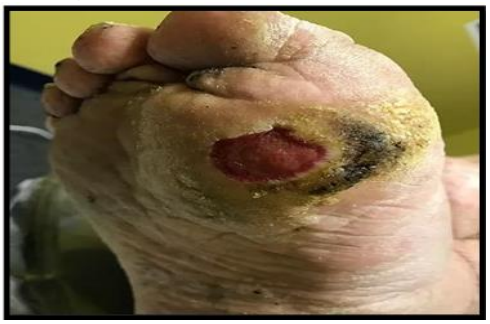
A traditional form of wound dressing is cotton gauze, which is widely used in clinical settings. However, it is not suitable for treating diabetic wounds because each dressing change causes painful secondary injury to the patient [4].

Different type of diabetic foot ulcers

Neuropathic foot ulcer: Neuropathic ulcers or diabetic foot ulcers are preventable ulcers associated with diabetes mellitus. These ulcers occur in the setting of unrecognized trauma, peripheral neuropathy, and foot deformities; however, they are often complicated by peripheral arterial disease and infection. Approximately 15% of individuals

with a neuropathic ulcer require limb amputation as a result of infection (Figure 2).
Neuropathic ulcerations arise from prominences from the internal structure, causing pressure point abnormalities on the external surface of an insensate body part. This is most commonly seen in the foot when pedal prominences cause pressure during ambulation. Due to the lack of sensation in the area, the patient is much less likely to be able to feel any pain or abnormalities in sensation associated with the ulceration.
Most neuropathic ulcerations occur on the lower extremity and affect prominent pedal surfaces such as the heel and metatarsal heads or areas of high friction prone to callus formation [5].

Figure 2. Neuropathic foot ulcer.



Ischemic foot ulcers

Ischemic means reduced blood flow to a part of the body. Ischemic ulcers are slow healing wounds. Usually found on the feet, ankles, or legs, they develop due to limited blood supply through the arteries to the legs. Ischemic ulcers are also known as arterial ulcers [6].
Ischemic ulcers are caused by limited blood flow from the arteries to the legs. Reduced circulation may be due to diabetes, inflammation, fat blockages, clogged arteries, Peripheral Arterial Disease (PAD), or infection. When blood does not reach the extremities, the area fails to get adequate oxygen and nutrients. This causes tissue damage and even cell death. The damaged, blood deprived tissue is unable to heal. If untreated, ischemic ulcers can lead to gangrene and limb loss (Figure 3).
A full medical history of the patient is evaluated. A wound specialist will examine the wound thoroughly and begin initial therapy. Laboratory testing and imaging studies such as non-invasive vascular studies, X-rays, CT and MRI scans may be performed to help diagnose the problems and develop a treatment plan. A multidisciplinary approach involving the staff of the centre, the primary care physician and specialists increases the likelihood of correct diagnosis, successful wound healing and prevention of complications or recurrence [7].

Figure 3. Ischemic foot ulcer.

Neuroischemic foot ulcers

An ulcer caused by diminished blood flow through an artery, esp. one that nourishes a finger or toe. These ulcers are usually found in patients with peripheral vascular disease. They may result in loss of digits as a result of gangrene. These foot ulcers occur in people who have both peripheral neuropathy and ischemia resulting from peripheral artery disease (Figure 4). Neuroischemic ulcers are least likely to heal without intervention and, if infected, the risk of amputation is high [8].

Common sites of neuroischemic ulcers: Toes, margins of the foot and the dorsum of the foot. This is the part facing upward when a person is standing up. Neuroischemic ulcers can also develop on the tips of toes and beneath overly thick toenails.

Appearance: Pale or yellow colour tissue that may have a halo of thin glassy callused skin. There can also be raised edges around the wound [9].

Figure 4. Neuroischemic foot ulcer.

Factors affecting diabetic foot ulcers

Wound site: The wound site is an important factor in wound healing because wound infection is a common cause of impaired wound healing [10].
Staphylococcus aureus and *Pseudomonas aeruginosa* are just a few of the organisms responsible for wound infections, and reports have indicated that *S. aureus* is the primary pathogen associated with diabetic foot infection.

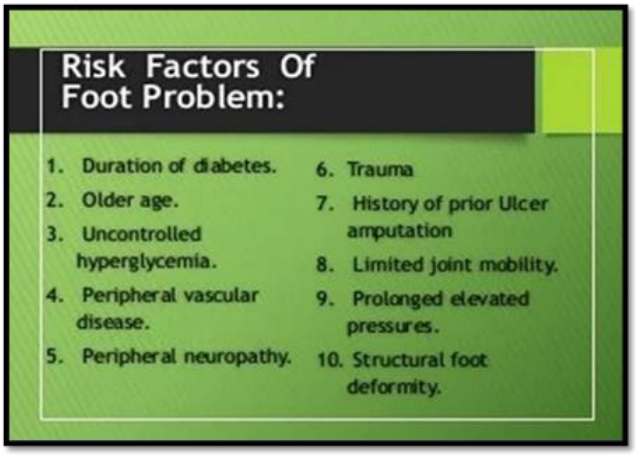
Immune state: Various components of the immune system are affected in diabetic patients. Polymorph nuclear leukocyte function has been reported to be reduced especially in the presence of acidosis, while leukocyte adhesion, chemo taxis, and phagocytosis may also be negatively affected in the diabetic state resulting in hence delayed healing [11-15].
The antioxidant systems that participate in bactericidal activity can be compromised in the diabetic state, leaving wounds in diabetic patients susceptible to infection.
Diabetes is a risk factor for bacteria in patients with pneumococcal pneumonia and is linked to increased mortality.

Disease state: *Aureus* and beta hemolytic streptococci are treated as pathogens in early diabetic foot infections. Studies have reported a higher incidence of bacterial infections in diabetic women than in non-diabetic women.
Diabetics seem to be more prone to wound infections. Greenhalgh reported a higher incidence (11%) of wound infections in diabetics than in the general patient population [16].

Reactive Oxygen Species (ROS): The high concentration of ROS could cause severe tissue damage that may lead to neoplastic transformation, further resulting in impaired healing process by inducing damage to cells, DNA, proteins and lipids.

Diet: Diet has been reported to affect wound healing. It has been observed that a serum albumin level of 3.5 g/dl or higher is required for adequate healing. Reduced protein levels could negatively affect collagen synthesis and thus impair wound healing (Figure 5) [17].

Figure 5. Factors affecting diabetic foot ulcer.



Mechanism of diabetic foot ulcer

The etiology of diabetic foot disease is multifactorial, and includes complications of diabetic neuropathy, vasculopathy, immunopathy, and poor glycaemic control. Diabetic neuropathy results in sensory, motor, and autonomic nerve dysfunction and is the most common cause of diabetic lower extremity ulcers. With proper screening, approximately 75% of diabetic patients undergoing foot and ankle surgery will be found to have neuropathy.

Because of an inability to determine injury or trauma, peripheral neuropathy is mostly associated with high rates of skin breakdown and neuropathic fractures. The inciting trauma could be caused simply by ill fitting shoes or minor sprains and strains. The risk of developing a first DFU has been shown to be 7 times higher in those with moderate or severe sensory loss compared to patients with preservation of sensation [18].

Without protective sensation, a neuropathic patient lacks the physical symptoms that would normally cue healthy individuals to examine or rest their feet, thereby increasing the extent of skin damage before presenting for treatment. Autonomic neuropathy also contributes to ulcer formation as it affects both physiologic secretions and the arteriovenous systems leading to dry, flaking, and fragile skin. This increases the risk for fissuring and skin breakdown, creating potential sites of infection [19].

Motor neuropathy can lead to structural changes to the foot. These changes are in part due to muscular imbalance and weakness caused by intrinsic atrophy, frequently manifesting as claw toes, hammertoes, prominent metatarsals, and other deformities.

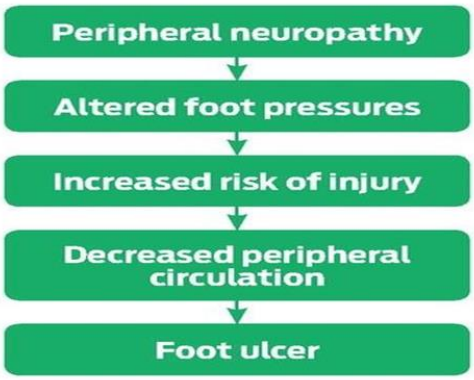
These deformities change pressure patterns on the foot making certain areas more susceptible to trauma or ulceration [20].

Peripheral Arterial Disease (PAD), which frequently coexists with neuropathy in the diabetic population and can cause difficulties with the feet. Nearly 50% of patients with diabetic foot disease also have PAD to some extent.

Individuals with DFUs are considerably more likely to have PAD, critical limb ischemia, and require revascularization than diabetic patients with Charcot neuropathy. Peripheral perfusion is reduced as a result of endothelial injury and vascular sclerosis in both large and small arteries.

Patients are more likely to develop ulcers as a result, and their capacity to heal wounds and fight infections is also compromised. Additionally, diabetes patients are less able to build an inflammatory response to infection (immunopathy). Patients neutrophil function, chemo taxis, phagocytosis, and t-cell response have all been observed to be impaired (Figure 6).

Figure 6. Mechanism of diabetic foot ulcer.



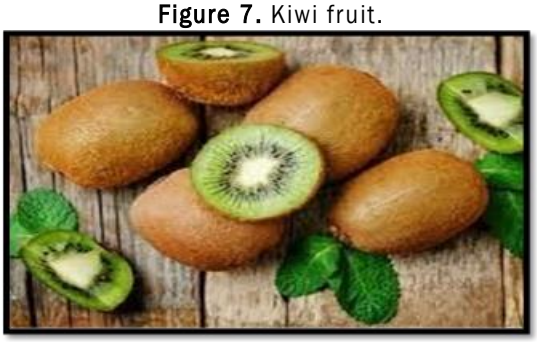
Different stages of diabetics foot ulcer

Traditional use of medicinal plants in diabetic foot ulcer: For over 5,000 years Egyptians, indigenous peoples of Africa, Asia, the Romans and the Americas have used medicinal plants as first line therapy for inflammation, burns, ulcers and surgical wounds.
They contain many natural bioactive compounds that help speed up the wound healing process and regenerate tissue at the wound site. Some examples of medicinal plants and their wound healing effects are listed below.

Kiwi fruit

The family Actinidiaceae, which has Chinese origins, includes the kiwifruit, *Actinidia deliciosa*. Kiwi fruit has been shown to have positive effects in healing burn wounds in a number of animal studies, including its usage in debridement and its proangiogenic and antibacterial qualities. The fruit's most significant component is the actinidin enzyme, which is comparable to the more popular protease, papain (from papaya fruit). The debridement abilities of kiwi are due to the cysteine protease actinidin.
A 3 mm thick layer of topical kiwifruit dressing was compared to standard therapy in a randomised, controlled clinical trial involving 37 patients with DFUs.
The standard of care included surgical debridement, ciprofloxacin 500 mg twice day, and clindamycin 600 mg three times daily (Figure 7).

Figure 7. Kiwi fruit.



Avocada

The *Persea Americana* (*P. Americana*) also known as avocado fruit belonging to the family Lauraceous. The fruit pulp contains monounsaturated fatty acids with the highest content of lutein. These play significant role in reducing the risk of cancer, wound healing and hepatoprotective action. It is also a rich source for vitamin A, Vitamin E, phospholipids and glycolipids.
Vitamin A is required for epithelial formation, cellular differentiation and immune function, and vitamin E is the major lipid-soluble antioxidant in the skin. Monounsaturated fatty acids, topical and systemic carotenoids and vitamin E promote wound healing.
Derivatives of phospholipids and glycolipids also found to have wound healing properties. Phytochemical screening of the *P. Americana* discovered the presence of flavonoids which are helpful in antioxidant property.
Extracts of *P. Americana* has shown both antifungal and antibacterial properties. Aqueous extract of *P. Americana* reported to have vasorelaxation depending up on the concentration.
This vasorelaxant effect may be produced by the inhibition of Ca^{+} mobilization through voltage dependent channels and to a lesser extent through receptor operated channels. *P. Americana* will show anti-Inflammatory activity by the inhibition of prostaglandin synthesis in platelets.
Extract of *P. Americana* significantly increases the rate of wound contraction/epithelialisation, and the weight of the granulation tissue.
These tissues are mostly composed collagen, oedema and new small blood vessels. The pro inflammatory activity of the constituents of *P. Americana* could attract macrophages to the wound site.
Macrophages stimulate the chemotaxis and proliferation of fibroblasts and attract endothelial cells to the wound and stimulate their proliferation to promote angiogenesis (Figure 8).

Figure 8. Avocada.

Papaya

Carica papaya (*C. papaya*), a member of the Caricaceae family. Flavonols, nicotine, tannins, and terpinenes are this fruit's primary phytochemical components, along with enzymes like papain and chymopapain.

Different plant parts have historically been employed in numerous treatments. Having potent bactericidal effects against bacteria is the *C. papaya* seed extract. *Shigella flexneri*, *Escherichia coli, Pseudomonas aeurginosa*, *Staphylococcus aureus*, and *Bacillus cereus*.

Their mature studies on several animals suggest that mature *C. papaya* fruit has anti-diabetic properties and humans. The effects of the C. *papaya* seed on blood sugar levels and/or diabetes have been well reported (Figure 9).

Figure 9. Papaya.

Turmeric

Turmeric (*Curcuma longa*) is an herb belonging to the family Zingiberaceae. Since from ancient time it was used as the coloring agent, dietary spice and as antibiotic. Rhizome (root) is the most important part of *C. longa* which is used as the ancient medicine for several diseases.

The paste of lime mixed with curcumin is used to treat inflammation and wounds, which is known to be one of the popular Indian home remedy *C. longa* consists of three principle curcuminoids, among which curcumin (diferuloylmethane 77%) is the major constituent. In more recent times, curcumin has been studied extensively for it uses as an anti-cancer anti-aging diabetic retinthy anti-infective and wound healing activity. Curcumin act against and protects the wound tissue from bacterial infections and induces cell proliferation.

It reduces inflammation to help in the restoration of damaged tissue. It acts as an ideal antioxidant as the free radicals are considered to be the major cause of inflammation during wound healing process of DFUs. The potency of curcumin in wound healing is attributed to its biochemical effects such as anti-infectious antioxidant and anti-inflammatory activities.

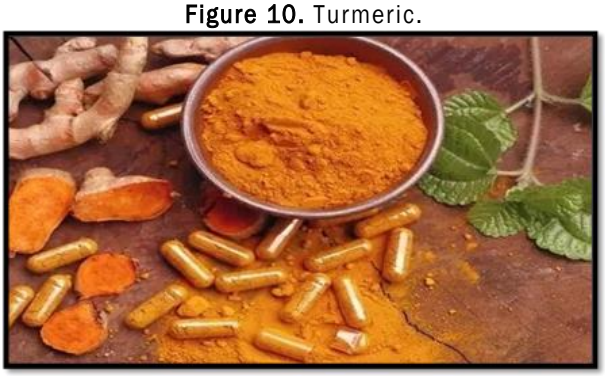
Curcumin also improves cutaneous wound healing by involving in the tissue remodeling, collagen deposition, and granulation tissue formation. The exact mechanisms by which curcumin modulates inflammation is by inhibiting the production of tumor necrosis factor alpha-α(TNF-α) and interleukin-1 (IL-1), two major cytokines released from monocytes and macrophages that play important roles in the regulation of inflammatory responses. Oxidative stress is a significant factor in the chronic wound healing process and generally inhibits tissue remodeling.

The as free radicals, ROS result in oxidative damage, DNA breakage and enzyme inactivation, leading to lipid peroxidation all of which inhibit optimum wound healing. ROS are considered to be the major cause of inflammation during chronic wound healing activity. It has been found that anti-oxidants with free radical scavenging potential like curcumin can significant prove wound healing when applied topically studied effect of curcumin (0.3%) in streptozotocinm induced dibabetic rats results revealed that topical curcumin application increased the wound contraction and decreased the expressions of inflammatory cytokines/enzymes *i.e.* TNF-α, Interleukin (IL)-1β and Matrix Metallo Proteinase-9 (MMP-9).

It also has shown increased levels of anti-inflammatory cytokine (IL-10) and antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase. Curcumin treated wounds showed better granulation tissue

dominated by marked fibroblast proliferation and collagen deposition, and thus wounds were covered by thick regenerated epithelial layer. These findings shown that the anti-inflammatory and antioxidant potential of curcumin caused faster and better wound healing in diabetic rats and they also further confirmed that curcumin could be an additional novel therapeutic agent in the management of impaired wound healing in diabetics (Figure 10).

Figure 10. Turmeric.



Giloy

The Menispermaceae family includes *Tinospora Cordifolia* (T. sinensis), also referred to as amritaorguduchi and the Rasayana plant in Ayurveda medicine.

The immunomodulatory properties of this plant species phytochemicals, including various terpenes, glycosides, alkaloids, steroids, and flavonoids, are thought to be the cause of its health advantages. *T. cordifolia* aqueous extract taken orally significantly reduced the need for surgical debridements in patients with DFUs in a randomised, double blind, placebo controlled clinical trial including 45 patients (P=.03).

However, the effects on bacterial clearance, neutrophil count, and ulcer size and depth were not statistically significant. It was proposed that polymorphonuclear cells considerable phagocytic activity augmentation acted as a regulator to encourage wound healing (Figure 11).

Figure 11. Giloy.

DISCUSSION

Olive tree

The olive tree, or *Olea europaea*, is a well-known evergreen tree with a large distribution in the Mediterranean region. It belongs to the family Oleaceae.

Numerous experimental experiments have shown that olive oil aids in the healing of chronic wounds. Olive oil may speed up the healing of burns, pressure ulcers, and cutaneous wounds by enhancing epithelialization, tissue blood flow, cell migration, and dermal reconstitution. It may also help to minimise inflammatory reactions. The main antioxidants in olive oil include oleic acid and phenolic substances like tyrosol and its derivatives, which can prevent oxidative damage and have anti-inflammatory effects in the healing of chronic wounds. A randomised, double-blind therapeutic trial involving 30 individuals with DFUs evaluated refined olive oil.

Daily topical application of olive oil was done for four weeks along with conventional therapy, and the outcomes were compared to a control group that received only conventional therapy. In comparison to conventional therapy alone, the use of olive oil considerably reduced the size (P=.01) and depth (P=.02) of the wound.

Additionally, 73.3% of the patients who had olive oil treatment had fully healed wounds, as opposed to just 13.3% of the patients in the control group (P=.003) (Figure 12).

Figure 12. Olive tree.

Kunth

Agelatina pithinchensis, (Kunth) which belongs to the Asteraceae family, is an important medicinal plant in traditional Mexican medicine. Aqueous extracts of A. pichinchensis protect skin lesions from fungal infection and have wound healing properties, as shown in several *in vitro* and *in vivo* studies. Anti-inflammatory effects on cell proliferation and stimulatory effects are attributed to the wound healing properties of this plant. Furthermore, the proliferative activity of the extract is mainly attributed to the flavonoid derivative 7-O-(β-D-glucopyranosyl)-galactic, suggesting that the flavonoid structure contributes to wound healing. Suggested to play an important role.

A randomized, double blind, controlled pilot study in 30 DFU patients to evaluate the efficacy and tolerability of A. pichinchensis as a topical wound healing agent.

An n-hexane/ethyl acetate extract of A. picinchensis was administered topically as a 5% cream formulation to patients in the study group, and control patients received 1% micronized silver sulfadiazine once weekly.

After 6 weeks, 77.5% of patients in the intervention group were cured compared to 69.8% of patients in the control group. Median time to wound healing was approximately 65 days in the intervention group and 77 days in the control group.

None of these results were statistically significant (P>0.05), but may have clinical value. Due to the incapacitating effect of DFU, the patient benefited from shortening her time to wound healing by 11 days.

In addition, this study compared herbal cream with silver sulfadiazine (which is the standard antimicrobial criterion, not a placebo), suggesting that the efficacy of the herbal cream meets the criteria for standard of care. The sample size of was relatively small. Larger studies are needed to further evaluate this treatment (Figure 13).

Figure 13. Kunth.

Aloe Vera

Aloe vera is botanical referred to as Aloe barbadensis (A. barbadensis) belonging to the family of Xanthorrhoeaceae.

A. barbadensis gel contains chemical constituents like saponins, naftoquinones, anthroquinones, sterols, and triterpenoids. These compounds are useful to point out beneficial effects (anti-inflammatory activity) and promote wound healing glucomannan, a mannose-rich polysaccharide, and gibberellin, a plant hormone, interact with protein

receptors of the fibroblast, thereby stimulating their activity and proliferation, which successively significantly increase collagen synthesis after topical administration of A. barbadensis gel.
This gel not only increases collagen content of the wound but also changes collagen composition (type III) and increases the extent of collagen cross linking.
Due to this, it accelerates wound contraction and increases the breaking strength of resulting connective tissue. A rise within the synthesis of hyaluronic acid and derma tan sulphate within the granulation of a healing wound following oral or topical application of A. barbadensis has been reported.
The mechanism involved in an exceedingly barbadensis in diabetic wound healing is by hydrolysing enzymes like prostaglandin, bradykinin, carboxypepditase and bard kinase that are hypothesized to scale back inflammation and pain A. barbadensis derived polysaccharides like mannose-6.
Potential use of herbal medicines within the treatment of diabetic foot ulcers, acemannan, another polysaccharide in an exceedingly barbadensis, has been shown to up regulate white somatic cell activity in the wound healing process.
Anti-bacterial properties of anthraquinones, an organic compound chargeable for the natural pigment of A. barbadensis, are beneficial in minimizing infections have studied the employment of A. barbadensis as gel base using Nitro-glycerine as active molecule in streptozotocin induced DFU and rat excision wound models.
They also further conformed that the gel (carpools 974p (1%) and *Aloe Vera*) treated animals promotes significant wound healing and closure in diabetic rats compared with the commercial product and provided a promising product to be utilized in diabetes induced foot ulcer (Figure 14).

Figure 14. *Aloe vera*.

Future prospect

Future prospect is needed to isolate, identify, and purify active ingredients in the plant extracts that are involved in foot ulcer processes in diabetic and non-diabetic conditions. Application of plant extracts as a possible adjuvant in the orthodox treatment of foot ulcer should be scientifically explored.
Large clinical trial on the use of medicinal plants in foot ulcer in diabetic and non-diabetic individuals should be conducted.
Therapeutic application of cytokines, growth factors and their soluble receptors could be studied to determine the extent of their involvement and acceptability in foot ulcer and treatment. Fibrotic processes are continuous and characterized by collagen synthesis, downregulation of degradative enzymes involved in removing scar tissue and fibrosis has been reported to be inhibited by antibodies, peptide receptor antagonists.
Research into interactions between fibrotic processes and antibodies could also provide useful information on foot ulcer.
A better understanding of the mechanisms of initiation, progression and resolution of foot ulcer could lead to the discovery of new therapies.
Despite limitations on the degree and extent of the applications of medicinal plants in the treatment of diabetic foot ulcer, it shows considerable promise and can indeed herald exciting new therapeutic strategies in diabetic foot ulcer.

CONCLUSION

Foot ulcer activities of medicinal plants in diabetic condition have recorded some appreciable efficacy as reported in this paper. Despite the limitations in terms of clinical trials, the majority of people especially in developing countries continue to depend on medicinal plants in the treatment of various diseases and infections including diabetic foot ulcer. In one particular case, the application of plant extract derived from medicinal plants prevented of infected diabetic foot ulcer from the amputation of the legs. Further research and clinical trials are recommended to confirm the efficacy and safety of specific medicinal plants and their mechanisms of action on diabetic foot ulcer.

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