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Title: An Overview: On the Potential Use Of Medicinal Plants In Diabetic Food Ulcer.

Jasbir Upadhyay[1] , Kajal Arvind Pradhan[2]
[1]*B. Pharm. Sem-7student, Smt. R. D. Gardi B. Pharmacy College, Nyara Rajkot, Gujarat, India.*
[2]*Assistant Professor, Smt. R. D. Gardi B. Pharmacy College, Nyara Rajkot, Gujarat, India.*

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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 thesetherapies are high. From longsince, many commonly used herbs and spices are claimed to have wound healing effects with various mechanisms. Hence their application inthe treatment of DFU may not only synergize the diabetic wound healing but also reduce the overall cost. This review discusses the possibleuse of herbs in treating DFUs with their mechanisms.
Keyword: Diabetes Mellitus, Diabetic foot ulcer, Diabetic neuropathy, Herbal.

I. INTRODUCTION

Figure 1.1: Diabetic Foot Ulcer

Diabetes mellitus (DM) is the major issue in the world wide and it is the chronic disorder

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which occurs due to the inadequate amount of insulin uptake (or) release. The occurrence of the DM is increased considerably. The main factors for the increasing DM are inactive lifestyle, obesity, ageing and in few cases it was genetically. The negligence of DM condition will result in a number of consequences which include neuropathy, retinopathy, endothelial dysfunction, atherosclerosis, myocardial infractions, diabetic foot etc. This results with many problems in foot such as neuropathy, peripheral arterial disease, DFU, osteomyelitis, gangrene and amputation. In the past decade the DM patients with leg complications are increased[1-3]. A major complication of this is diabetic foot having ulcer healing difficulties, which are clinically significant and challenging. It was estimated that approximately 15% of total diabetic patient will be affected by DFU. DM is considered as the major cause of non-traumatic lower extremity amputation that reduces the survival of patient and cause huge burden to the society. To improve the healing process of a DFU, there are several Medicinal Plants (Alovvera ,Curcumin , and Tinosporacordifolia) are used . Apart from this the treatment of DFU using a single strategy may unlikely less effective since DFU arises as a consequence of multi-factorial pathologies. To overcome these hurdles herbal compounds can be used which are biocompatible, biodegradable and less ornon-toxic. Several extracts of plants, minerals and animal origin are described in the traditional texts of Indian systems of medicine like “Ayurveda” for their healing properties under the term ‘Vranaropaka’. Some of these plants have been screened scientifically for the evaluation of their wound healing activity in different pharmacological models and human subjects. Plant constituents and herbal extracts are known to be the rich source of anti-oxidants to counter act Reactive Oxygen Species (ROS). Hence antioxidants are helpful in treating many diseases such as arteriosclerosis, inflammatory disorders, cancer, coronary disease and DM. Hence natural

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antioxidants due to their free radical scavenging property gives possible protection against many chronic diseases as well as lipid per oxidation . The herbs also enhance the rate of tissue healing by providing different vital substances (vitamins, proteins and minerals) required at different stages of wound regeneration and proliferation. Herbals are also found to be safe and cost effective than allopathic drugs. This review discusses the possible use of herbs in treating DFUs with their mechanisms.

II. DIFFERENT TYPE OF DIABETIC FOOT ULCERS

[2.1]Neuropathic Foot Ulcer

Figure 2.1.1:Neuropathic Foot Ulcer

Occur where there is peripheral diabetic neuropathy, but no ischemia caused by peripheral artery disease. [1] .Are also caused by the loss of protective sensation in combination with structural changes and repeated trauma/pressure to the foot. [15]

[2] ISCHEMICFOOT ULCERS

Figure 2.2.1 : Ischemic Foot Ulcer

[2] Ischemic Foot Ulcers

[3]NeuroischemicFootUlcers

Figure 2.2.3 :Neuroischemic Foot Ulcer

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.[14,15]

III. FACTOR AFFECTING DIABETIC FOOT ULCER

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.[14,15]

Factor Affecting Diabetic Foot Ulcer

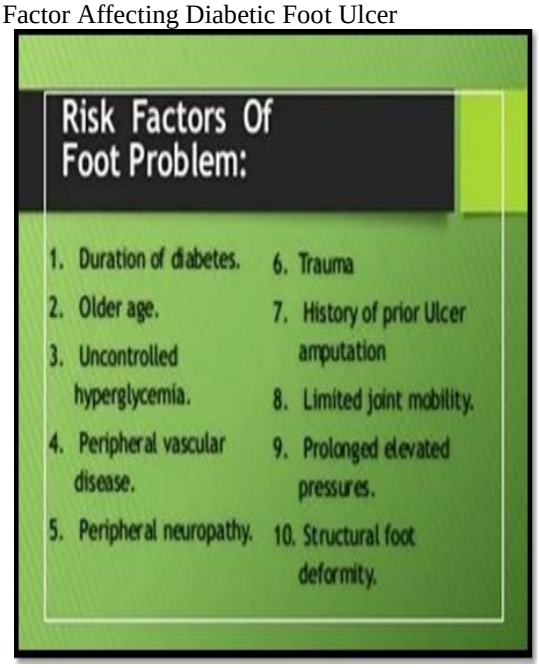

Figure 3 :Factors Affecting Diabetic foot ulcer

Figure 3.1: Factor Affecting Diabetic Foot Ulcer

[1]Wound sites

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The wound site is an important factor in wound healing because wound infection is a common cause of impaired wound healing[22,23].

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[33-36] .

[2] Immune state

Various components of the immune system are affected in diabetic patients. Polymorphonuclear leukocyte function has been reported to be reduced especially in the presence of acidosis, while leukocyte adhesion, chemotaxis, and phagocytosis may also be negatively affectedin the diabetic state resulting in hence delayed healing.

The antioxidant systems that participate in bactericidal activity can be compromised in the diabetic state, leaving wounds in diabetic patients susceptible to infection [41].

Diabetes is a risk factor for bacteria in patients with pneumococcal pneumonia and is linked toincreased mortality[18,43]

[3] Disease State

Aurous and beta-haemolytic 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[44]

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.

[4] Reactive Oxygen Species (ROS)

The high concentration of ROS could cause severe tissue damage that may lead to neoplastic transformation, further resultingin impaired healing process by inducing damage to cells, DNA, proteins and lipids[12,17] .

IV. MECHANISM OF DIABETIC FOOT ULCER

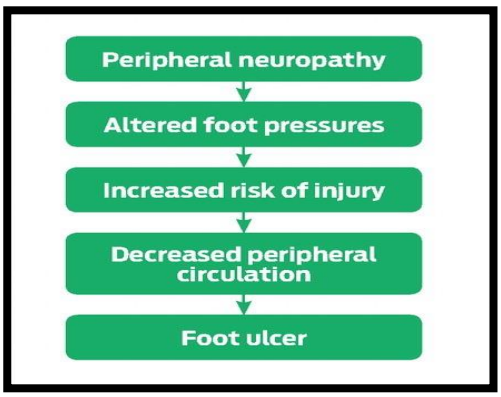


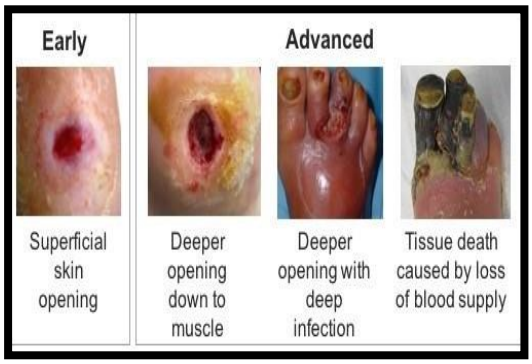
Figure 4.1 : Mechanism ofDiabetic foot ulcer

The etiology of diabetic foot disease is multifactorial, and includes complications of diabetic neuropathy, vasculopathy, immunopathy, and poor glycemic 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[2] .

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 orsevere sensory loss compared to patients with preservation of sensation[14] .

V. DIFFERENTS STAGES DIABETIC FOOT ULCER



5.1 Different stages of Diabetic Foot Ulcer

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VI. TRADITIONALUSE OF MEDICINAL PLANTS IN DIABETIC FOOT ULCER

For over 5,000 years Egyptians, indigenous peoples of Africa, Asia, theRomans 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 woundhealing process and regenerate tissue at the wound site. Some examples of medicinal plants and their

wound healing effects are listed below.

[6.1] Actinidadeliciosa (kiwi fruit) [

Figure 6.6.1 :Actinidadeliciosa

The family Actinidiaceae, which has Chinese origins, includes the kiwifruit, Actinidiadeliciosa.Kiwifruit 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 [29]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 kiwiare due to the cysteine protease actinidin[24,].

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.

[6.2]Avocada

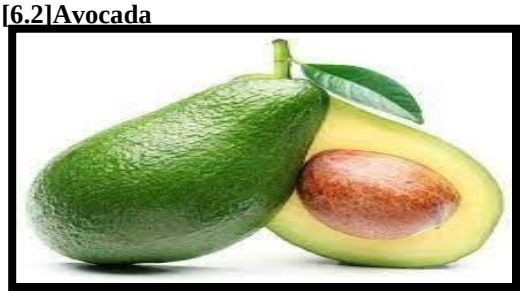

Figure 6.6.2 :Avocada

The Persea Americana (P. americana) also known as avocado fruit belonging to the family Lauraceae. The fruit pulp containsmonounsaturated fatty acids with the highest content of lutein. These play significantrole in reducing the risk of cancer, Wound healing andhepatoprotective action .It is also a rich sourcefor vitamin A, Vitamin E, phospholipids and glycolipids[14] .

Vitamin A is required for epithelial formation, cellular differentiation and immunefunction, and vitamin E is the major lipid-soluble antioxidant in the skin. Monounsaturated fatty acids, topical and systemic carotenoids andvitamin E promote wound healing[36] .

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 ofP. americana has shown both antifungal and antibacterial properties. Aqueous extract of P. Americana reported to havevasorelaxation depending up on the concentration.

This vasorelaxant effect may be produced by the inhibition of Ca+ mobilization throughvoltage-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[26] .

Extract of P. americana significantlyincreases the rate of wound contraction/epithelialisation, and the weight of the granulation tissue[29].

The pro-inflammatory activity of the constituents of P. americana could attract macrophages to the wound site[34].Macrophages stimulate the chemotaxis and proliferation of fibroblasts and attract endothelial cells to thewound

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and stimulate their proliferation to promote angiogenesis[22].

[6.3] Papaya

Figure 6.6.3 : 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[54] .

Different plant parts have historically been employed in numerous treatments. Having potent bactericidal effects against bacteria is the C. papaya seed extract.Shigellaflexneri, Escherichia coli, Pseudomonas aeurginosa, Staphylococcus aureus, and Bacillus cereus[46].

Their matureStudies on several animals suggest that mature C. papaya fruit has anti- diabetic properties andhumans. The effects of the C. papaya seed on blood sugar levels and/or diabetes have been well reporte [42] .

[6.4]Curcumin

Figure 6.6.4 :Curcumin

Turmeric (Curcuma longa) is an herb belonging to the family Zingiberaceae. Since from ancient time it was used as the coloring agent, dietaryspice and as antibiotic [45,55] .Rhizome (root) is the most important part of C. longa which is used as the ancient medicinefor several diseases.

The paste of lime mixed with curcumin is used to treat inflammationand 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[54] .In more recent times, curcumin has been studied extensively for ituse as an anti-cancer anti-aging diabetic retinthyanti-infective and wound healing activity Curcumin act against and protects the wound tissuefrom bacterial infections and induces cell proliferation.[14]

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[21] .The potency of curcumin in wound healing is attributed to its biochemical effects such as anti-infectious antioxidant and anti-inflammatory activities.

Curcuminalso improves cutaneous wound healing by involving in the tissue remodeling, collagen deposition, and granulation tissue formation[42]. 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 ofinflammatory responses[46]. Oxidative stress is a significant factor in the chronic wound healing process and generally inhibits tissue remodeling[21] .

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 healingactivity [19] .It has been found that anti-oxidants with free radical scavenging potential like curcumin can significantprove wound healing when applied topically studied effect of curcumin (0.3%) in streptozotocin-inducedDibabeticrats.

The results revealed that topical curcumin application increased the wound contraction and decreased the expressions ofinflammatory cytokines/enzymes i.e. TNF-α, interleukin (IL)-1β and matrix metalloproteinase-9 (MMP-9). It also has shown increased levels ofanti-inflammatory cytokine (IL-10) and antioxidant enzymes (superoxide dismutase, catalase and glutathione

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peroxidase)[36] .Curcumin treatedwounds showed better granulation tissue dominated by marked fibroblast proliferation and collagen deposition, and thus wounds werecovered by thick regenerated epithelial layer. These findings shown that the anti-inflammatory and antioxidant potential of curcumin causedfaster and better wound healing in diabetic rats and they also further confirmed that curcumin could be an additional novel therapeutic agentin the management of impaired wound healing in diabetics [42] .

[6.5] Tinosporacordifolia

Figure 6.6.4: Tinosporacordifolia

The Menispermaceae family includes TinosporaCordifolia (T. sinensis), also referred to as amritaorguduchi and the Rasayana plant in Ayurvedic 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[51]. T. cordifolia aqueous extract taken orally significantly reduced the need for surgical debridements in patients with DFUs in arandomised, double-blind, placebo-controlled clinical trial including 45 patients (P =.03)[39].
However, the effects on bacterial clearance, neutrophil count, and ulcer size and depth were not statistically significant.

[6.6] Oleaeuropaea

Figure 6.6.6 :Oleaeuropaea

The olive tree, or Oleaeuropaea, is a well-known evergreen tree with a large distribution in the Mediterranean region. It belongs to the family Oleaceae[34].

Numerous experimental experiments have shown that olive oil aids in the healing of chronic wounds. Olive oil may speed up the healing ofburns, pressure ulcers, and cutaneous wounds by enhancing epithelialization, tissue blood flow, cell migration, and dermal reconstitution. It may also help to minimise inflammatory reactions[41,12] . 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[48]. A randomised, double-blind therapeutic trial involving 30 individuals with DFUs evaluated refined olive oil[55].

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[52] . 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)[54].

[6.7]AgeratinaPichinchensis

Figure 6.6.7 :AgeratinaPichinchensis

Agelatinapithinchensis, which belongs to the Asteraceae family, is an important medicinal plant in traditional Mexican medicine. Aqueous extracts of A. pichinchensis protect skin lesionsfrom fungal infection and have wound-healing properties, as shown in several in vitro and in vivo studies[47] . Anti-inflammatory effects on cell

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proliferation and stimulatory effects are attributed to the wound-healing properties of this plant[48] . Furthermore, the proliferative activity of the extract is mainly attributed to the flavonoid derivative 7-O-(β-D-glucopyranosyl)-galactin, suggesting that the flavonoid structure contributes to wound healing. suggested to play an important role[49].

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[52]

.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[53] .

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[31] .

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 [32]. Larger studies are needed to further evaluate this treatment[35] .

[6.8] Aloe vera

Figure 6.6.8 : Aloe vera

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

A. barbadensis gel containschemical constituents like saponins, naftoquinones, anthroquinones, sterols, and triterpenoids. These compounds areuseful to point out beneficial effects (anti-inflammatory activity) and promote wound healing Glucomannan, a mannose-richpolysaccharide, and gibberellin, a plant hormone, interact with protein receptors of the fibroblast, thereby stimulating theiractivity and proliferation, which successively significantly increase collagen synthesis after topical administration of A. barbadensisgel[42] .

This gel notonly increases collagencontent of the wound but also changes collagencomposition (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 ofhyaluronic acid and dermatansulfate within the granulation of a healing wound following oral or topical application of A. barbadensishasbeen reported. [43] .

The mechanism involved in an exceedingly. barbadensis in diabetic wound healing is by hydrolyzing enzymes like prostaglandin, bradykinin, carboxypepditase and bardykinase that are hypothesized to scale backinflammation and painA. barbadensis derived polysaccharides like mannose-6[44].

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 activityin 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 Nitroglycerin as active molecule in streptozotocin-inducedDFU and rat excision wound models[46].

They also further conformed that the gel (carbopol 974p (1%) and Aloe vera) treatedanimals promotes significant wound healing and closure in diabetic rats compared with the commercial product and provided a promisingproduct to be utilized in diabetes-induced foot ulcer[45] .

VII. FUTHER PROSPECT

Further Propect is needed to isolate, identify, and purify active ingredients in the plant extracts that are involved in wound healing

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processes in diabetic and non-diabetic conditions[46]. Application of plant extracts as a possible adjuvant in the orthodox treatment of wounds should be scientifically explored[47].

Large clinical trial on the use of medicinal plants in wound healing in diabetic and non-diabetic individuals should be conducted[51].

Therapeutic application of cytokines, growth factors and their soluble receptors could be studied to determine the extent of their involvement and acceptability in wound healing 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[52,53].

Research into interactions between fibrotic processes and antibodies could also provide useful information on wound healing[54].

A better understanding of the mechanisms of initiation, progression and resolution of wound healing 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 wounds, it shows considerable promise and can indeed herald exciting new therapeutic strategies in wound healing[55].

VIII. CONCLUSION

Wound healing 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 wounds. In one particular case, the application of ointment derived from medicinal plants prevented of infected diabetic wound 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 wound healing.

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