

Medicinal herbs: Why to include in diabetic foot ulcer therapy? A review

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ABSTRACT

Diabetic foot ulcers (DFUs) are a main diabetes hurdle that causes significant morbidity and mortality. In the first 12 months, mortality rates related with the development of DFUs which are predicted to be 5%, and 5-year mortality rates are estimated to be 42%. In DFU management, surgical debridement, dressings to maintain a moist wound environment and exudate control, wound off-loading, vascular evaluation, infection, and glucose control are all typical practices. Even with this thorough strategy, the results of DFUs can still be improved. To lower DFU healing times and rate of amputation, several adjuvant therapies have been investigated. Herbal drugs belonging to family Lamiaceae, Caricaceae, liliaceae, Meliaceae, Zingiberaceae, Actinidiaceae, Myrtaceae, Lauraceae, Vitaceae, etc., have chemical constituents which develop the wound healing fast and promotes epithelization of skin. Species of these families such as *Rosmarinus officinalis*, *Carica papaya*, *Aloe vera*, *Ampelopsis japonica*, *Paeonia suffruticosa*, *Azadirachta indica*, *Syzygium cumini*, *Hylocereus undatus*, *Calendula officinalis*, *Curcuma longa*, *Actinidia deliciosa*, and *Aegle marmelos corr. Pennel* are beneficial in management of DFU as their chemical constituents are known for the wound healing mechanism. These drugs have major constituent Rosmarinic acid, Papain, Naftoquinones, Nimonin, zingiberene, Curcumin, ascorbic acid, Methylglyoxal, Vitamin A, Vitamin E, and Oligomeric, procyanidins respectively. These constituents have antioxidant, anti-inflammatory, antimicrobial, antibacterial, and anti-diabetic action; thus, all these drugs have efficient application in the of diabetic foot ulcer's management.

Keywords: Diabetes, Wounds, Healing, Infection, Herbal drugs, Diabetic foot ulcer

Introduction

Type 1 diabetes is caused by faulty glucose sensing or insulin secretion, type 2 diabetes is caused by insufficient compensatory insulin resistance, and type 1 diabetes is caused by autoimmune-mediated cell death.^[1] The link between diabetes and diabetic complications is known as hyperglycemia. It is caused by a lack of glucose control. Hyperglycemia and dyslipidemia are two serious diabetic side effects connected to secondary complications such as macro- and microvascular issues.^[2] Hyperglycemia increases protein glycosylation, whereas glucose oxidation makes free radicals that oxidize low-density lipoproteins or boost membrane lipid lipoperoxidation, causing damage to cellular membrane.^[3] The growth of both macro- and microvascular problems, as

well as diabetes-related infections, has resulted in an increase in diabetes morbidity and mortality.^[4] Diabetic wounds are sluggish to heal, difficult to control, and can linger for weeks, making them a severe clinical challenge to manage. The specific pathophysiology of poor wound healing in diabetic wounds remains unknown.^[5] Human and animal studies, on the other hand, reveal impairment at various stages of the wound healing process. Inadequate wound healing management, especially in low-resource settings, can progress to diabetic foot ulcers (DFUs) and even amputation, yet authorized growth factor and cell treatments for DFUs and other diabetes-related wounds are seldom accessible throughout treatment. Nature, on the other hand, has provided a platform for medicinal substances to cure a variety of maladies and disorders, including diabetic wounds.^[6] It is important to note that many current therapeutic chemicals derived from medicinal plants are employed in traditional therapy. Furthermore, a resurgence of interest in the use of medicinal plants as effective and safer alternatives in the management of various infections, including diabetic wounds, has been sparked by a variety of factors, including bacterial resistance, environmental degradation and pollution, as well as irrational use of orthodox medicines.^[7] The use of

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medicinal plants to cure ulcers, boils, sores, and wounds is common knowledge and practice in many cultures. The clinical trial found that using two herbal formulations in DFU patients averted limb amputation in 85% of cases.^[8] Scientists are investigating the function of medicinal plants to assess their potential wound healing properties and extract molecules associated to wound healing due to the existence of bioactive compounds in plants.^[9] In this review research, the impact of medicinal herbs on wound healing in diabetics is studied.^[10]

Pathogenesis of DFU

In diabetics, the foot serves as a crossroads for a variety of disease processes, as it contains practically all of the lower limb's components, including skin, subcutaneous tissue, muscles, bones, joints, nerves, and blood vessels.^[11] DFUs are more typically the result of DFI than the cause. These infections frequently start with a break in the dermal envelope, commonly at a site of mechanical/thermal damage or ulceration.^[12] Infection is described as the entrance of microorganisms into host tissues, where their proliferation causes inflammatory reactions. Following it, tissue breakdown occurs.^[13] Infection in soft-tissue or bone below the malleoli in a diabetic individual is characterized as DFI. Neuropathy, vasculopathy, immunopathy, and foot biomechanics are all variables that predispose diabetic individuals to having a DFI.^[14] Debridement must be careful, and it is typically required to debride many times. The following are the treatment priorities:^[15] (1) Aggressive infection treatment, (2) ischemia identification and evaluation for potential revascularization, (3) pressure alleviation on the wound, and (4) wound environment improvement with debridement dressing and advanced care therapies. A complex DFU can be treated in a variety of ways. An artery Doppler ultrasonography can be used after a thorough ulcer examination, which includes measurements, X-rays, and funduscopy.^[16]

Factors that Slow Down the Process of Healing in DFU

Following are the factors which prolongs the process of wound healing.

Age

It is the major factor, there appears to be a link between an individual's age and the wound healing process.^[15] Wound healing appears to be slower as people get older. This could be because fibroblast growth and activity decline with age, whereas collagen synthesis and wound contraction are similarly bringing down in geriatric persons who are injured.^[16]

High blood sugar levels

Blood sugar levels are the most important factor in determining how quickly a wound heals. When blood sugar levels are greater than usual, nutrients and oxygen are unable to energize cells, your immune system is unable to work properly, and inflammation in the body's cells increases. These side effects inhibit wound healing.^[16]

Neuropathy

Sugar levels in blood generally more than normal might also result in peripheral neuropathy. The nerves and arteries are impaired

with time. This might create numbness in the infected regions. The hands and feet are particularly prone to neuropathy. It's possible that you won't be able to feel the wounds when they happen.^[16] This is one of the main reasons why diabetics are more likely to get foot wounds.

Poor circulation

Diabetes patients are more likely to develop peripheral vascular disease, which is characterized by impaired circulation. Patients with peripheral artery disease had a 49.7% prevalence of type 2 diabetes. Blood arteries in the limbs constrict as a result of peripheral vascular disease, reducing blood flow. The disease also inhibits the capacity of red blood cells to efficiently flow through channels. Furthermore, a more-than-usual glucose level of blood thickens the blood, impairing the blood flow of body even more.^[15]

Immune system deficiency

Many persons having diabetes may show problems in initiating their immune systems. The number of fighter cells of immune deployed to cure wounds, as well as their ability to perform, is commonly reduced.^[16] If the immune system is not working properly, wound healing is hindered and the risk of infection is raised.

Infection

If the immune system working improper, the body may struggle to combat infection-causing microorganisms. Infection is also more likely when blood sugar levels are higher than normal.^[15] Because bacteria thrive on the excess sugar in the bloodstream, this is the case. High blood sugar levels can also make it difficult for immune cells to fight off microorganisms. If the infection is not treated and allowed to progress, it can lead to gangrene or sepsis.^[16]

Wound healing is assumed to be the consequence of a complicated chain of cellular and biochemical events that end in the renovation of functional, structural and increased strength in injured tissues.^[17] Wound healing normally progresses in a predictable and time-related way. Any disturbance in the wound healing process has the potential to result in chronic wounds or pathological scarring. There are a number of variables that influence wound healing, and a thorough study of these factors and their potential impact on wound healing might aid in the development of therapeutic agents for wound healing in diabetes and non-diabetic patients.

Treatment of DFU

The three main issues that must be addressed in the therapy of DFUs are debridement, unloading, and infection control.^[15-17]

Debridement

All periwound callus, foreign substances, and necrotic tissue are eliminated during debridement, leaving only viable tissue. To limit, debridement is essential because to the risk of infection and periwound pressure, which may hinder normal wound contraction and healing.

Offloading

The most effective method of unloading for treating a foot ulcer is to use a wheelchair or crutches to entirely minimize weight bearing on the affected foot. Total contact casts are difficult and time-consuming to administer, but they significantly decrease wound pressure and have been found to heal 73–100% of all wounds.

Infection control

Polymicrobial infections are common in limb-threatening diabetic foot infections. Bacteria that are resistant to the antibiotic methicillin *Staphylococcus aureus*, -hemolytic streptococci, enterobacteriaceae, *Pseudomonas aeruginosa*, and enterococci are all common infections. In mixed infections with aerobes, anaerobes such as bacteroides, peptococcus, and peptostreptococcus are seldom only pathogens. although they can be encountered in mixed infections with aerobes. Antibiotics are antibiotics that are used to treat infections.

Herbal Remedies/Drugs

Many different plants and herbs have been recognized as having wound-healing effects, with known and unknown mechanisms and chemical contents.^[16] The use of therapeutic herbs in ulcer heal therapy and care includes, debridement, and disinfection the creation of an environment conducive to natural healing. Medical plant ingredients are regarded to be less toxic and have fewer adverse effects than typical therapeutic drugs, which explains the renewed interest in medicinal plant use and use in wound healing, both in diabetic and non-diabetic circumstances.^[17] Wound healing in diabetes is impaired is regarded as a major health issue by medical specialists all over the world, and it is occasionally associated to a non-specific cause. As a result, one of the therapeutic options for therapy, particularly in low-resource areas, is the use of medicinal plants. Here are some of the plants that have wound-healing properties.

Rosmarinus officinalis

The drug includes complete areal plant of *R. officinalis* belonging to family Lamiaceae.^[18] This plant is well-known for its antibacterial and antioxidant properties. 1, 8-cineol, camphor, α -pinene, linalool, camphene, and limonene that these are the chemical constituents of the drug having strong anti-inflammatory action.^[19] According to some experiments, aqueous extract of this drug on topical application promoted wound healing of DFU in rats.^[20,21]

Carica papaya

The drug includes fruit of *C. papaya* family caricaceae. Extract of fruit had been said to have antibacterial, anti-inflammatory, and antioxidant properties.^[22] Its major chemical constituents are carpaine and pseudocarpaine, proteolytic enzymes quimiopapain and papain and benzyl isothiocyanate.^[23] In a study, the diabetic experimental group's animal was treated externally with *C. papaya* extract, and wounds were measured on days 1, 5, and 11 for all groups. The scientists found that rats treated with fruit extract had a considerable growth in wound healing process.^[24] When compared to animals in control group, a

shorter epithelialization period and a higher proportion of wound contraction in the excision wound model found.^[25]

Aloe vera

It is obtained as areal part of plant *Aloe barbadensis* family Liliaceae. *A. vera* had been identified and utilized in conventional medicine in several nations around the world to treat a variety of illness problems.^[26] It had been demonstrated to have anti-diabetic, anti-inflammatory, and antibacterial properties.^[27] In an *in vivo* investigation, male Wistar rats were utilized to assess the wound restorative activities of the herbal extract.^[28] Excision and incision wounds were made, and the wounds were treated with *A. vera* extract on particular days. The number of days required for complete epithelialization of the wound was denoted as the duration of epithelialization.^[29] After day 4, the collagen level in granulation tissues skyrocketed. Its positive effects on many stages of wound healing, such as fibroplasia, collagen production, and contraction, result in quicker healing in treated animals than in untreated animals.^[30]

Ampelopsis japonica

It consists of roots of *A. japonica* family Vitaceae. *A. japonica*, a plant near to eastern Asia and eastern North America, has long been used to cure burns, ulcers, and other illnesses. *A. japonica* has pharmacological qualities such as neuroprotection, antibacterial activity, and anticancer activity.^[31] Ethanol extracts of dried roots of *A. japonica* expedited the recovery of cutaneous scald injury in rats, according to a research. Tumor necrosis factor-alpha (TNF) and tumor growth factor-1 levels were shown to be greater 2 days after injury and then gradually reduce as healing continued.^[32] Interleukin (IL)-10 levels, on the other hand, have been shown to increase after 14 days, which is when the wound closes.^[33] Ethanolic *A. japonica* improved reepithelization, granulation tissue development, vascularization, and collagen deposition when compared to wounds treated with Vaseline (petroleum jelly) or silver sulfadiazine.^[33]

Paeonia suffruticosa

It is obtained from plant *P. suffruticosa* family Paeoniaceae. *P. suffruticosa* contains antioxidant, neuroprotective, antitumor, anti-inflammatory, and antidiabetic effects, according to pharmacological research. *P. suffruticosa*'s dried root is widely applied to damaged skin to aid healing and ease discomfort.^[32] Gallic acid, 1,2,3,4,6-O-pentagalloyl glucose, paeoniflorin, and oxypaeoniflorin are active ingredients.^[34] In a study, it is seen that *P. suffruticosa* arouses the survival and propagation of human primary dermal fibroblasts and keratinocytes *in vitro* at low doses implying its possible application as a wound healing treatment.^[33,35]

Azadirachta indica

It is obtained from *A. indica* family Meliaceae. The principal chemical elements of neem include nimbolin azadirachtin, quercetin, sodium nimbinate, nimbidin, nimbidol, gedunin, savanna, and nimbin.^[36] It is antibacterial, anti-inflammatory, and anti-diabetic herb.^[37] In some studies, performed on rats and other animals, it is shown that neem extract fastens the wound healing of DFU due to antibacterial activity.^[38] It also reduces inflammation and promotes healing.^[39]

S. cumini

It is obtained from fruits and seeds of plant *S. cumini* family Myrtaceae. delphinidin 3,5-diglucoside, cyanidin 3,5-diglucoside, petunidin 3,5-diglucoside, peonidin 3,5-diglucoside, delphinidin 3-glucoside, malvidin 3,5-diglucoside, delphinidin acetyl-diglucoside, peonidin-3,5-diglucoside, and petunidin 3-glucoside are chemical constituents of *S. cumini*.^[40] The jamun's bark and fruit both have therapeutic benefits. *S. cumini* possesses anti-inflammatory and antibacterial characteristics, which aid in the reduction of edema and inflammation associated with DFUs. Anti-diabetic effects are also found in *S. cumini*.^[41] This helps to maintain blood sugar levels in check and prevent ulcers from worsening. It also aids in the purification of the blood and the treatment of foot ulcers. Black Plum is often used to treat a wide range of illnesses, particularly diabetes and its consequences. The plant contains numerous chemicals that have been identified as plant characteristics. Seed was used to carry out pharmacological activities on diabetes.^[41] There are not many studies on the pharmacological effects of Black plum phytochemical ingredients. Based on these findings, the author analyzed the role of Black Plum in a range of treatments and suggested that, further, clinical and phytochemical research be conducted on the plant to develop safer medications.^[42]

Holocereus undatus

It is obtained from *H. undatus* family Cactaceae. This plant, which has huge fragrant blossoms that emerge only at night, is widely dispersed in Brazil and is said to serve a significant function in food and conventional medicine.^[43] Its leaves and blossoms, in particular, are utilized as a hypoglycemic agent. The extract of leaves, flowers, and fruits were employed in the experiment to test the plant's wound healing qualities.^[44] In diabetic rats, topical treatments of the plant extract resulted in a considerable boost in the healing process.^[43] Wounds cured with 0.5% the flowers and leaves extract revealed a substantial rise in strength in diabetic rats as compared to the control group. In comparison to the untreated control, the collagen content of granulation tissues in wounds treated with the flower extract increased significantly. According to the research, topical use of water extracts of leaves as well as flowers resulted in considerable wound healing activity.^[43,44]

Calendula officinalis

It is flower of *C. officinalis* family Asteraceae. Calendula is a homeopathic remedy that can help DFUs in a variety of ways.^[45] This homeopathic treatment is made from a flowering plant known as "Pot Marigold." Calendula is most effective when used topically to treat DFUs. Calendula gels or sprays applied directly to a DFU give excellent outcomes and speed wound healing.^[46] The anti-inflammatory, antioxidant, and anti-microbial properties of calendula extract are all beneficial. As a result, the homeopathic medicine helps to prevent and treat infections in DFUs. Calendula decreases the foot ulcer's bad odor and promotes the formation of new tissues, resulting in speedier healing. Calendula flowers (quercetin and isorhamnetin) include natural chemicals such as triterpene saponins, triterpene alcohols (amyryns and faradiol), and flavonoids (quercetin and isorhamnetin).^[46] The photoprotective effect of topical

formulations is thought to be due to an increase in collagen production in the subepidermal connective tissue. Compounds in calendula have been shown to encourage new tissue development and decrease inflammation in wound healing. Early study suggests that applying a calendula spray in addition to routine care and cleanliness can help persons with DFUs prevent infection and reduce odor.^[47]

Curcuma longa

Curcuma (Zingiberaceae) is a genus of perennial rhizomatous plants that are intrinsic to subtropical to tropical climates. Curcuma cultivation is widespread in Asia, Australia, and South America's tropical and subtropical climates.^[29] It has been used to cure disorders such as skin diseases, stress, infection, and depression in India and China since ancient times. The rhizomes are the most important part of the plant, and the curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) are the most active components. Curcuminoids are non-toxic polyphenolic compounds with varied therapeutic actions, including the formation of powerful immunosuppressants that inhibit IL-2 and IL-12 synthesis.^[48] TNF, IL-1, IL-6, and IL-8 are among the pro-inflammatory cytokines inhibited by this drug, as are inducible nitric oxide synthase, cyclooxygenase-2, lipoxygenase-5, and a number of others. Curcuminoids may also regulate apoptosis and minimize neurotoxic effects in lipopolysaccharide-stimulated macrophages and alveolar monocytes. It also reduces the NF- κ B pathway-induced inflammatory pattern by inhibiting I κ B phosphorylation and degradation while activating the receptor mechanism activated by peroxisome proliferator.^[49] *C. longa*, the turmeric plant that is often used as a spice in cooking, has been recognized by scientists. Orange tuberous rhizomes distinguish this plant, which is widely recognized and farmed throughout Southeast Asia.^[49] Since ancient times, it has been employed in these areas as a natural medicinal medication for a variety of pathological disorders. The presence of curcumin, which has antioxidant and anti-inflammatory qualities, is a distinguishing feature of this plant. Curcumin likely helps to prevent and treat a variety of ailments due to its antibacterial, anti-diabetic, anti-viral, and anticancer properties.^[48]

Actinidia deliciosa

It is the fruit of *A. deliciosa* family Actinidiaceae. The antibacterial and proangiogenic properties of kiwifruit (*A. deliciosa*) have been demonstrated. Ascorbic acid and proteolytic enzymes (actinidin) are also present. This research looked at the benefits of Kiwifruit on the healing of neuropathic DFUs in clinical settings. On the basis of macroscopic, microscopic, and microbiological status, the ulcers were investigated and evaluated. Biopsies of the ulcers were obtained before and after the interventions to conduct microbiological and histological analyses. The antibacterial and proangiogenic properties of kiwifruit (*A. deliciosa*) have been demonstrated. Additional proteolytic enzymes (actinidin) and ascorbic acid are also present.^[50] The properties of Kiwifruit on the healing of neuropathic DFUs in clinical settings were investigated. Protein-dissolving enzymes (Actinidin) and other natural chemicals found in kiwifruit improved various aspects of wound healing. We conclude that using kiwifruit in the management of neuropathic DFUs is a straightforward, adaptable, effective method based on these advantages, and safety concerns. Many biological investigations have been conducted, and various preparations have

been explored, to improve the DFU healing process. Various herbal substances for ulcer healing have been created in Africa and Asia over the last century. The kiwifruit is a fruit that originated in China and had been known there for over 700 years.^[51] This fruit is thought to contain strong protein-dissolving enzymes that is actinidin, ascorbic acid (scavenging agent), antibacterial compounds, and hence can aid in the healing of ulcers. The kiwifruit has been shown to have established properties in ulcer debridement, angiogenesis, and disinfection in several *in vitro* and animal investigations.^[51]

Aegle marmelos corr. Pennel (Bael)

It is fruit of plant *Aegle marmelos* corr. Pennel family Rutaceae. Numerous phytochemicals, such as phenolics, carotenoids, pectins, alkaloids, flavonoids, tannins, coumarins, and terpenoids, have been found in significant concentrations in *A. marmelos*, according to scientific investigations.^[52] Similarly, several bioactive substances have been extracted and identified from those groupings. Aegeline, aegelinosides, marmelin, marmelosin, aegelenine, malondialdehyde, anhydromarmeline, and marmelide are the most notable isolated chemicals that have been discovered to elicit significant bioactivity. It contains alkaloids, polysaccharides, beta carotene, antioxidants, Vitamin C, Vitamin B, and a variety of other biochemical compounds. Tannins, calcium, phosphorus, iron, protein, and fiber are also present.^[53]

Conclusion

DFUs are a source of concern for the world's expanding diabetic population, herbal drugs discussed in this review article are beneficial in management of DFU.

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