Review Article

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# A Comprehensive Review on Diagnosis and Management of Diabetic Foot Ulcers with Possible Ayurvedic and Herbal Remedies

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**ABSTRACT**

Diabetes, a silent killer and globally renowned disease, has enormously afflicted most parts of the world causing serious health issues to an individual. The aetiology of these ulcers includes high glucose levels, improper foot hygiene, etc. The pathophysiology of diabetic foot ulcers involves oxidative stress to the nerve tissues and other complications leading to loss of sensation in the patient's feet. Many times, diabetes remains undiagnosed but the foot ulcers can be evaluated by the latest electrodiagnostic, radiological, or vascular studies. Once identified, they can be treated with several topical antibiotics and certain foot assistance methods. Besides allopathic medication, a large number of medicinal plants and phytochemicals are commonly employed as supportive therapy which possesses anti-oxidant, anti-bacterial, and other potent therapeutic properties enhancing the wound healing process as per its physiology and with minimal side effects. Ayurvedic formulations are also widely used in the treatment of diabetic foot wounds. Therefore, the present review aims to address the most commonly used diagnostic methods as well as the treatment of diabetic foot wounds. The article specifically reviews herbal plants *Phellodendron chinense*, *Angelica dahurica,* and *Moringa oleifera* and Ayurvedic formulations like *Jatyadi Ghrita* and *Triphala* for their effectiveness in treating diabetic foot remission.

**Keywords:** Diabetic foot ulcer, Herbal, Ayurveda, *Phellodendron chinense, Angelica dahurica*

## 1. Introduction

Diabetes, is one of the most prevalent diseases across the world, affecting around one-third of the population in the world, and a major source of welcoming certain dreadful health conditions in most individuals. Multiple factors such as a sedentary lifestyle, genetic factors, more sugar intake, altered glucose metabolism, etc. contribute to diabetic foot ulcer. Diabetes adversely affects health causing a surge in body weight, cardiac abnormalities, oxidative stress, and other irregularities, and one of these situations includes inordinate skin ailments occurring in the foot of the insulin-resistive person, known as diabetic foot ulcer. It is a very common open sore that occurs as a complication in approximately 15 per cent of diabetic patients, which might lead to lower extremity amputation [1,2].

In this condition, a breakdown occurs in the tissues of the foot's skin, and layers present underneath the skin are vividly exposed [3]. Vascular insufficiency and decrement in leucocyte function accompany these ulcers with infection, which might vary from simple cellulitis to further chronic osteomyelitis, followed by frequent hospitalization [4].

It is difficult to manage them with routine exercise, diet, or insulin treatment, but more than three-fourths of amputation is prevented if it is diagnosed at early stages and suitable treatment is been catered to the patient [5]. Doctors may classify ulcers on basis of the Wagner Ulcer Classification System as given in Table 1 [6].

### *1.1. Aetiology*

Knowing the aetiology of a disease simplifies the aspect of treatment. In the case of diabetic foot ulcers, many factors contribute to it, such as high blood glucose levels retard the healing process, poor blood circulation accompanied by nerve damage, underlying peripheral neuropathy, foot deformities, as shown in Figure 1, ill-fitting footwear, poor maintenance of foot hygiene, hypertension, and dyslipidaemia. About 60% of diabetic patients are prone to neuropathy which further may lead to foot ulcers. Individuals having a flat foot are good candidates for foot ulcers, as there is inordinate stress throughout their foot, which ultimately causes tissue inflammation in high-risk areas of the foot [3,4,8].

### *1.2. Pathophysiology*

Hyperglycemic conditions are the major contributor to diabetic foot ulcers, where oxidative stress is

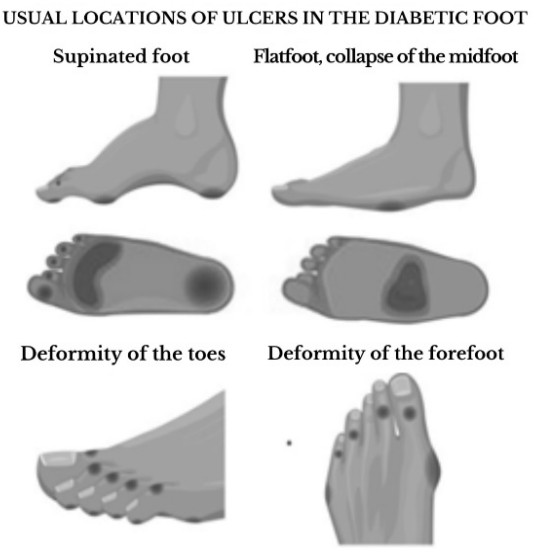


**Figure 1.** Foot deformities causing foot ulcer [7]

**Table 1.** Wagner Ulcer Classification System

| Grade | Characteristic |
|---|---|
| 0 | no open lesions; may have healed lesion |
| 1 | superficial ulcer without penetration to deeper layers |
| 2 | deeper ulcer reaching tendon, bone, or joint capsule |
| 3 | deeper tissues involved with abscess, osteomyelitis, or tendonitis |
| 4 | gangrene in a portion of the forefoot or heel |
| 5 | extensive gangrenous involvement of the entire foot |

produced in the nerve cells, further giving rise to neuropathy. Neuropathy is a critical factor usually accompanied by vascular and immunological components. Complications give rise to ischemic conditions where the aforementioned harm to nerve cell proteins involves their glycosylation followed by nerve impairment. Further pathophysiology incorporates the casualty to the motor neurons leading to disparities between flexors and extensors, and autonomic deformities. The autonomic nerve bearing the damage further leads to dysfunction of sweat glands causing severe dryness to that part of the skin followed by cracks in the outer dermal region and tearing of the skin. The nervous damage causes chronic foot ulcers as the requirement of blood to that particular area is insufficient to maintain an intact skin texture, causing the inability of that individual to sense the pain of any stimuli. Also, there is an elevation in thromboxane A2 levels which is an agonist of platelet aggregation and a vasoconstrictor giving rise to plasma hypercoagulability. In addition to all of this, slow healing due to diabetic conditions induces complications such as gangrene, cellulitis, osteomyelitis, and sepsis which might lead to amputation of the lower limb [8,9,10,11].

### *1.3. Evaluation*

Three different established techniques are utilized for detecting the peril of foot ulcers in diabetic patients, this includes neuropathy, the pressure of the foot, and circulation [12]. Nerve conduction studies are a type of electrodiagnostic study which in addition to specific physical examination is employed for differentiating several types of neuropathy, which is a primary candidate in the evaluation of diabetic foot ulcers. This sort of technique is very specific in the detection of peripheral neuropathy [9]. Laboratory examinations can be done such as erythrocyte sedimentation rate, complete blood count, fasting blood sugar, etc. Radiological aid can also be taken which includes X-rays and MRIs, that detect osteomyelitis (inflammation of the bone caused by infection), and entrapment of air in the subcutaneous region [9]. Suspected peripheral neuropathy can also be identified with the help of ankle-brachial index (ABI) in association with an arterial doppler. The ABI determines the ratio of the systolic blood pressure in the arm and the ankle [13]. Besides these tests, the probe-to-bone test can also be employed to detect osteomyelitis which is an invasive method generally used to suspect an infection caused by bacteria [14]. Several latest techniques used for the detection of ulcers are sophisticated, faster, and more accurate, one of which is a prototype model called as WoundVue® system, where the principle of stereophotogrammetry is applied. This technique enables the health practitioner to assess the wound on a three-dimensional scale. It aids to measure the area, volume, and maximum depth of the ulcers with commendable accuracy. The WoundVue® employs two infrared cameras as shown in Figure 2 [15] which capture the wound images and construct a 3D-based structure through a process of triangulation as given in Figure 3 [16].

This technique requires minimum human resources and expertise and a major advantage is that it does not create any sort of contact with the wound for obtaining better results [17].

Another contemporary approach is the YOLO technique. This technique is an algorithm-based model which detects real-time objects and transmits them into a regression formula. In this technique, a specific neural network is used which helps to determine bounding boxes and class probabilities from the full image [18].


**Figure 2.** Infrared cameras that are efficient in developing a 3D image [15]


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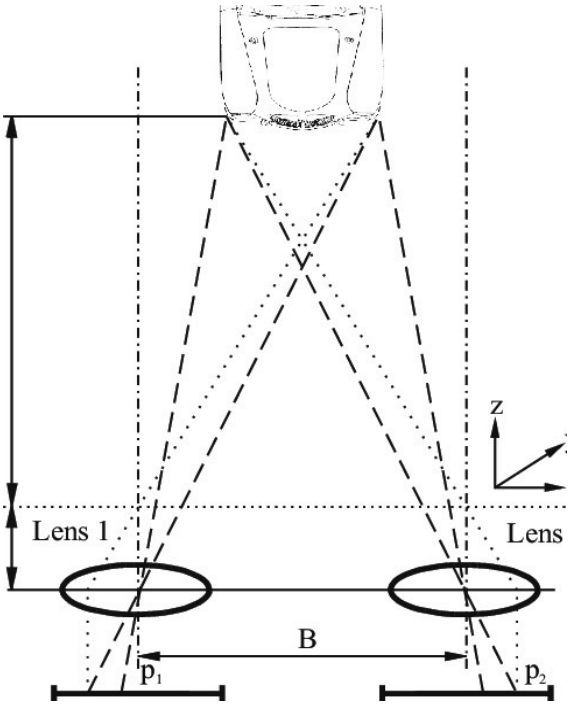


**Figure 3.** Triangulation process for 3D image creation [16]

### *1.4. Prevention or Management of foot ulcers*

Firstly, blood sugar levels should be within normal levels and agents which elevate cholesterol and blood sugar levels should be strictly avoided such as alcohol, tobacco, etc. The second effort to prevent ulcers should be taking proper care of the feet for any sort of injuries such as cracks, redness, cuts, infections, blisters, or bruises [1]. Irrational medications should not be used to treat these abnormalities; instead, trained medical professionals should be concerned. [4]. Educating the individuals is also a part of preventive medication, this includes imparting knowledge to the patient and professionals. Primarily, the caregivers must educate themselves and then administer preventive or necessary treatment to the patients [19].

The latest technique that contributes to the management of foot ailments fascinatingly is the inception of the smart sensor. This approach integrates the cloud technologies in smartphones and links them to the sensors present in the soles which regularly assess the weight, and overall foot condition of the person and update the physicians regarding the patient's health. On a preventive note, doctors can be aware of the patients by using this technique, and they can also assist them in preventing the ulcers from becoming uncontrollable. This method is very practical, accurate, portable, and compatible with smartphones [20].

### *1.5. Treatment*

The main course of treatment involves keeping the feet clean and avoiding infection. It also involves preventing the condition from getting worse. But, recognizing the symptoms such as pain, inflammation, fever, observation of purulence as well as any sort of infection, ensures the foot ulcers that need to be treated, followed by treating the neuropathic cause (two-fold approach) [3,9]. The angiogenesis process is also a necessary part of ulcer healing which indeed is dependent on modulating several signalling pathways by angiogenic substances such as Akt, endothelial nitric oxide synthase, extracellular signal-regulated kinase 1/2, and endothelial nitric acid [21]. For healing, imperative wounds should immediately take aid from an experienced physician or a dermatologist which can be a better decision in preventing the situation to get worsen. In the preliminary stage, the health professional tries to pluck out the ulcer along with some foreign particles or some debris that might be the etiological factor for the foot ulcers [9]. The caregiver also focuses on the type of dressing which is generally a moist type creating an environment to enhance the management of wound exudates [22]. If an infection is determined by histopathological studies, then the concerned doctor prescribes certain antimicrobial treatments to the patient [9]. This treatment includes the oral combination of cephalosporins and amoxicillin-clavulanic acid that is generally prescribed but if the laboratory or biopsy reports demand Methicillin-resistant *Staphylococcus aureus* based treatment, then the medication should include linezolid, clindamycin or cephalexin plus doxycycline or a trimethoprim-sulphamethoxazole combination. The anaerobic spectrum regime includes quinolones (ciprofloxacin), or cephalosporins (ceftriaxone, ceftazidime). After this treatment, many patients ought to seek a doctor's medical attention as the wounds might enter the next phase of peripheral vascular disease where the damaged part lacks blood supply and hence the oxygen demand, therefore to counteract it, hyperbaric oxygen therapy is catered to the patient which accelerates the healing of the diabetic foot ulcers [3]. Certain wounds which are deep or are the case of osteomyelitis, require in-

tense debridement with minimal surgery. Many foot ulcers bring excess pain in the patient which can be treated by administering pregabalin and duloxetine as first-line medication, only if the concerned doctor advises to [18].

In today's modern world, many innovations are available one of which is Low-Level Light Therapy (LLLT). This technique involves low-intensity light sources such as lasers of low power or light-emitting diodes which aid in rendering cellular functions and molecular pathways to promote the healing phases that include inflammatory, proliferative, and remodelling. In brief, this technique targets cells' redox-sensitive transcription factors. The LLLT method is less invasive, easy to carry, economic, etc. [23,24].

A very recent advanced wound care dressing material MaxioCel® is been introduced by an Indian startup named Axio Biosolutions, which might be a game-changer in the treatment aspect of diabetic foot ulcers. The chitosan-based product has been tested for a variety of uses, including the treatment of bed sores, vascular ulcers, diabetic foot ulcers, and other chronic wounds. It uses bioactive microfibre gelling technology [25]. It has specific properties in the treatment of diabetic wounds such as exudate management, acceleration of wound healing, hemostats, and pain reduction [26]. The product is an excellent absorbent antimicrobial dressing candidate which also caters to improvement in scar formation [27]. MaxioCel® serves multiple benefits such as intact adherence to the applied part, no loss of product integrity, and painless detachment with minimal medical assistance [25].

At last, patients should maintain better health of their feet, and adopt off-loading techniques like the assistance of walkers, customized shoes of therapeutic intention, or padding to the insoles [3,28].

## 2. Medicinal plants used to treat diabetic foot ulcer

Before the arrival of allopathic medication or the era where synthetic chemical agents were used to treat particular diseases, herbal treatment for healing a specific disease was the prime option. Even in a tech-savvy world, the herbal approach is opted for by many patients, to remove the disease from its root cause rather than treating it temporarily. For diabetic foot ulcers, many herbal plants cater to healing properties which include, *Rosmarinus officinalis* L., *Annona squamosal* L., *Carica papaya* L., *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., *Moringa oleifera* Lam., *Catharanthus roseus* (L.) G. Don., *Rehmannia glutinosa* (Gaertn.) DC., *Centella asiatica* (L.) Urb. , *Martynia annua* L., *Punica granatum* L., and *Phellodendron chinense* C. K. Schneid. Most of these plants create an environment that naturally starts healing the wounds without causing any hypersensitive reactions. In addition to it, they also have properties that include anti-inflammatory, antibacterial, angiogenesis, tissue regeneration, etc. In a diabetic ulcer rat model, a couple of these plants were also found to be responsible for minimizing the levels of advanced glycation end products (AGE), which are responsible for limiting the binding of AGE to its receptor by creating negative feedback and hence reducing oxidative stress. In addition, they also deaccelerate Protein-tyrosine Phosphatase (PTP1B) expression levels which may lead to improvement in insulin activity and hence increase glucose uptake [29,30].

The article specifically reviews herbal plants *Phellodendron chinense, Angelica dahurica,* and *Moringa oleifera* and ayurvedic formulations like *Jatyadi Ghrita* and *Triphala* for their effectiveness in treating diabetic foot remission.

### *2.1. Phellodendron chinense C. K. Schneid.*

It is a highly effective medicinal plant from the Rutaceae family that is found in Northeast and Southwest China and is known as "Huang bai" in Chinese. The medicinal part of the cortex is collected from its trunk bark and further dried. It is known for its commendable therapeutic effect such as anticancer, hypotensive, antimicrobial, anti-gastric ulcer, antioxidant, etc. The phytochemicals include limonoids which serve as an anti-inflammatory, quercetin is effective for coronary artery disease, and other constituents like phenolic acid and quinic acid possess potent therapeutic action [31]. A study including randomized clinical trials by showed satisfactory results of the cortex part of the plant and other two associated ingredients in specifically treating diabetic foot ulcers systematically by removing necrosis, escalating the process of granulation, and reducing the amputation to a smaller extent [32]. During the *in vitro* experiments, it was found that certain microbial species such as *Streptococcus viridans, Streptococcus pneumoniae, Staphylococcus aureus,* and *Corynebacte-*


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*rium diphtheriae* are found to be sensitive to Huang bai. Along with antibacterial activity, it is also helpful in terminating swelling, and stimulating certain growth factors in the entire wound healing process to direct some physiologic effects, induction of apoptosis, and enhancing angiogenesis process, proliferation, and differentiation. For healing the wound, it is necessary to elevate the serum Vascular endothelial growth factor (VEGF) and basic Fibroblast Growth Factor (bFGF) levels, as they contribute to enhancing vascular growth and angiogenesis for tissue rejuvenation, and accelerate wound healing. In this study, it was observed that the experimental group which was treated with cortex of *P. chinense* was found to elevate serum VEGF and bFGF levels [33]. *P. chinensis* has also been efficient in providing antioxidant properties by fabricating the AKT/NF-κB pathway in zebrafish embryos [31], which might produce the same effect in humans when applied topically.

### *2.2. Angelica dahurica (Hoffm.) Benth. & Hook. f. ex Franch. & Sav.*

It is also a Chinese medicinal plant from the *Umbelliferae* family, whose roots have impressive therapeutic use such as in supraorbital pain, acne, rheumatism in China, Japan, and Korea, ulcer, and some vascular diseases (due to its vasorelaxant effect). *Angelica dahurica* consists of some phytochemicals such as oxypeucedanin, imperatorin, byakangelicol, isoimperatorin, and byakangelicin [34]. The ethanolic extract of *A. dahurica* aids in proliferating the synthesis of nitric oxide in endothelium. Its constituent imperatorin might counteract ischemic-induced apoptosis via activating ERK pathways. The research determined the VEGF expression was stimulated during the angiogenic process in their experimental subject. Their *ex vivo* and *in vivo* experimental study observed that the ethanolic extract of *A. dahurica* was found to be efficient in the proliferation of new blood vessels and also employing pericyte which is necessary for diabetic foot impairment. Also, the study found that the ethanolic extract of this plant can be a potent ingredient in intensifying inflammation resolution by reducing IL-1β and TNF-α which are inflammatory cytokines. In addition, the study showed an increment in collagen I deposition, which might improve fibroblast function [21]. In past studies, *A. dahurica* root water extract promoted angiogenesis and accelerated wound healing in db/db mice via the HIF-1α/PDGF-β signaling pathway at the dose of 1.8g/kg (Figure 4). The same extract also found to form a network of tubes on HUVECs (human umbilical vein endothelial) cell lines under a hypoxic environment at the concentration of 200 µg/ml [35].

The study also observed that *A. dahurica* is effective in collagen deposition as well as in arranging collagen in an orderly manner. They found surface receptor glycoproteins CD32 and CD146 double positive in the diabetic wound when treated with *A. dahurica* in comparison to the non-*A. dahurica*-treated wound [35].

### *2.3. Moringa oleifera Lam.*

A study conducted on a hyperglycemic animal model utilizing the leaves of *M. oleifera* (Moringaceae family) showed specific characteristics such as modulation of inflammatory mediators, improved wound contraction, and epithelialization [36]. Table 2 contains detailed properties of *M. oleifera* in treating diabetic foot ulcers. *M. oleifera* contains some essential phytochemicals such as tannins, triterpenoid, flavonoid, and alkaloids which may be responsible for antimicrobial properties as well as astringent properties that aid in wound contraction and enhances the rate of epithelialization. The aqueous fraction of *M. oleifera* is helpful to combat certain bacterial species such as *Pseudomonas aeruginosa, and S. aureus* [37]. A recent study on Wistar rats scientifically proved that the flavonoids present in *M. oleifera* imitate insulin and can almost cause the uptake of

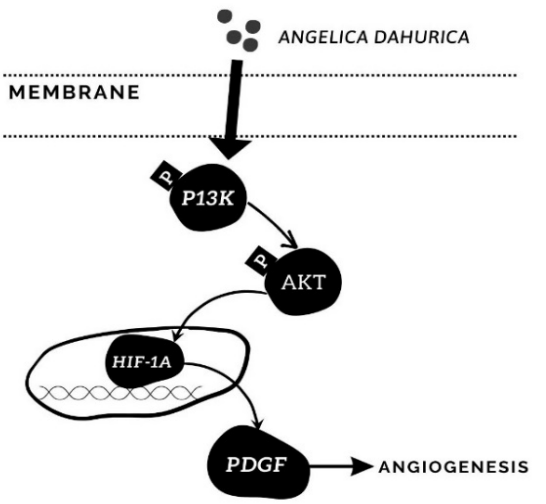


**Figure 4.** Angiogenesis pathway modulation by A. dahurica [35]

**Table 2.** Properties of 2% aqueous extract of *M. oleifera* in treating diabetic foot ulcer in animal experimentation [37]

| Properties |
|---|
| Antibacterial properties |
| Minimizing wound size |
| Anti-inflammatory response |
| Increase the contraction of wound |
| Enhances the angiogenesis process |
| Improvement in the formation of granulation tissue |
| Improves collagen deposition and regeneration of tissues |

glucose in the peripheral tissues, imparting anti-diabetic properties. Flavonoids present in the plant also contribute to carbohydrate metabolism by promoting the expression of rate-limiting enzymes involved in carbohydrate metabolism. In diabetic conditions, there is damage caused to the β-cells, which is also proven in this study, where the methanolic extract of *M. oleifera* is found to be useful in mitigating oxidative protein stress by enhancing the protein content of the pancreas [38].

### *2.4. Ayurvedic approach*

*Vimlapanakarma* is an initial part of the Ayurvedic herbal treatment offered to the patient to neutralize or control the inflammation, which is done by sensitizing the cellular structure around the affected part. This form of treatment maintains and keeps the extracellular fluid matrix intact, which is necessary for wound healing. Also, it helps to improve wound inflammation and blood circulation near the infected part of the ulcer. In this method, gentle massage is done with the thumb and finger around the affected area with the required herbal oil [39].

*Jatyadi Ghrita* is a traditional Ayurvedic formulation that works well on a variety of wound types as an antibacterial, fungicidal, and wound healer [40]. *Jatyadi Ghrita*, a powerful ingredient is derived from multiple plant sources such as *Trichosanthes dioica* Rox*., Azadirachta indica* A. Juss*., Hemidesmus indicus* R. Br*., Myristica fragrans* Houtt*., Terminalia Chebula* Retz*.,* etc. [41]. Several phytochemicals are obtained in the evaluation of *Jatyadi Ghrita* such as tannins, phytosterols, essential oils, etc. [40] In an animal study, it has been observed that this ingredient intensifies the hydroxyproline, protein, and hexosamine content in affected tissue. This ingredient is more effective than mupirocin hydrochloride at speeding up the maturation of granulation tissue, reducing inflammatory cells, and inducing early angiogenesis and is also a potent competitor of silver sulfadiazine in early tissue epithelialization [41].

*Triphala* is also an Ayurvedic medicament that is obtained by drying the fruits of *Terminalia bellirica* (Gaertn.) Roxb., *Terminalia chebula* Retz., and *Emblica officinalis* L. [40]. When *Triphala* is poured with a liquid on the body, it is known as *Vrana Prakshalana* (washing the affected part) in Shashtiupkrama and it aids in lesion healing and purification. It also possesses anti-inflammatory properties and eliminates endotoxins and caters to analgesic and antiulcerogenic effects by plunging down the effect of nitric oxide free radicals *in vitro*. In a case study of a Grade IV diabetic foot ulcer category patient, a treatment comprising *Triphala* and *Jatyadi Ghrita* was administered and a significant reduction in bacterial load was observed [41].

## 3. Plausible formulations for the treatment of diabetic foot ulcers

### *3.1. Hydrogel*

Hydrogels are the best possible formulation which can be effective and cater to the needful herbal ingredients to the impaired site of the patient. Also, the hydrogels are high in water content which intercepts the drying of the affected wound site and due to a higher concentration of water, they automatically


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lyse the infected cells leading to improvement of the damaged site [42]. Preparing a formulation with the necessary quantity of the extracts of the above-discussed four plants can be optimum if added with the ideal excipients. The primary reason for preparing the herbal hydrogel is the herbal active ingredients that are less reactive and give minimal side effects to the skin. In addition to it, hydrogels are cost-effective and can give a cooling effect to the patient which may act as an analgesic remedy. Hitherto, no such combined herbal formulation has been presented in the treatment of foot ulcers in diabetic patients.

### *3.2. Aerosol*

The most appropriate formulation for this kind of condition is one that is contactless, less expensive, and has a delivery system that disperses the medication as a mist. According to an open-label, randomised control trial using aerosol formulation can be effective in reducing index ulceration and accelerating the epithelialization of the foot's skin [43]. As a hypothesis, one can prepare a suspension of the aforementioned herbal extracts of *P. chinense, A. dahurica,* and *M. oleifera* that can be sprayed on the affected areas of the feet, as shown in Figure 5 [44], can be effective and might give the sufferer a breakthrough. Aerosols also leverage the healing time and reduce the total cost of treatment and the smaller size of particles of this drug delivery system directly targets the affected part and penetrates deep into the skin of the patient's foot. Also, the drug inside remains contamination-free, as direct contact is terminated with the external environment due to its closed system, and the first-pass metabolism of the drug is also skipped compared to oral antibiotics [45]. Thus, all these points sum up making aerosol a healthy formulation candidate in the systematic treatment of diabetic foot ulcers.

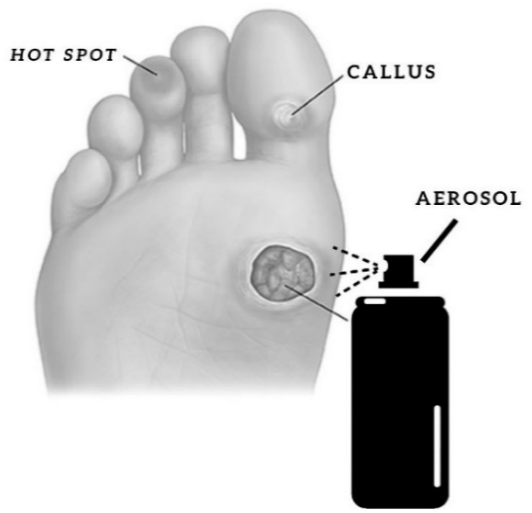


**Figure 5.** Aerosol application in treatment of diabetic foot ulcers [2, 44]

## 4. Conclusion

A diabetic foot ulcer is a serious health ailment and needs sincere medical attention, also in the near future the overall cost of the treatment of these wounds might surge. Hence, herbal remedies serve the cause by catering efficiently to the damaged parts, reducing the treatment cost, and eliminating the chances of bacterial resistance. The aforementioned properties of *P. chinense, A. dahurica*, and *M. oleifera* can be effective in the healing of foot ulcers along with the Ayurvedic approach, as many of the characteristics of these remedies are relevant in the systematic healing of wounds giving relief to the patients. Considering the multiple advantages of the hypothetical formulations (hydrogel and aerosol), blending the above-mentioned herbal active ingredients may be competent in healing diabetic foot ulcers against the conventional remedies and may be the recent ones.

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## Conflict of interest

The authors declare no conflict of interest.

## Statement of Contribution of Researchers

Content compilation and manuscript design - H.J.T. , Review, editing, and revision of the final manuscript – P.R.B.

## References


1. Frequently Asked Questions: Diabetic Foot Ulcers, Michigan Medicine.; [cited 2022 August 8]. Available from: https://www.uofmhealth.org/conditions-treatments/podiatry-foot-care/frequently-asked-questions-diabetic-foot-ulcers [Website]
2. Diabetic foot ulcer.; [cited 2022 August 13]. Available from: https://toticell.com/diabetic-foot-ulcer [Website]
3. Diabetic Foot Ulcers.; [2022 August 13]. Available from: https://www.healthline.com/health/diabetic-foot-pain-and-ulcers-causes-treatments [Website]
4. Kuo YS, Chien HF, Lu W. *Plectranthus amboinicus* and *Centella asiatica* Cream for the Treatment of Diabetic Foot Ulcers. Evid Based Complement Alternat Med. 2012;2012:1–9.
5. Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. Am Fam Physician. 1998;57(6):1325–32, 1337–8.
6. Shah P, Inturi R, Anne D, Jadhav D, Viswambharan V, Khadilkar R, et al. Wagner's Classification as a Tool for Treating Diabetic Foot Ulcers: Our Observations at a Suburban Teaching Hospital. Cureus [Internet]. 2022 Jan 22 [cited 2023 May 20]; Available from: https://www.cureus.com/articles/82780-wagners-classification-as-a-tool-for-treating-diabetic-foot-ulcers-our-observations-at-a-suburban-teaching-hospital
7. Diabetic Foot Ulcers- Symptoms, Causes, and Risk Factors - Pristyn Care: [cited 2022 August 15]. Available from: https://www.pristyncare.com/blog/diabetic-foot-ulcers-symptoms-causes-risk-factors-pc0441/ [Website]
8. Rosyid FN. Etiology, pathophysiology, diagnosis and management of diabetics' foot ulcer. Int J Res Med Sci. 2017;5(10):4206.
9. Neuropathic Ulcer.: [cited 2022 August 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559214/ [Website]
10. Aumiller WD, Dollahite HA. Pathogenesis and management of diabetic foot ulcers. JAAPA 2015;28(5):28–34.
11. Clayton W, Elasy TA. A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients. Clin Diabetes. 2009;27(2):52–8.
12. Bharara M, Cobb JE, Claremont DJ. Thermography and Thermometry in the Assessment of Diabetic Neuropathic Foot: A Case for Furthering the Role of Thermal Techniques. Int J Low Extrem Wound. 2006;5(4):250–60.
13. Ankle-Brachial Index Use in Patients with Diabetes : Advances in Skin & Wound Care.: [cited 2022 August 14]. Available from https://journals.lww.com/aswcjournal/Citation/2004/04000/Ankle_Brachial_Index_Use_in_Patients_with_Diabetes.8.aspx [Website]
14. Lam K, van Asten SAV, Nguyen T, La Fontaine J, Lavery LA. Diagnostic Accuracy of Probe to Bone to Detect Osteomyelitis in the Diabetic Foot: A Systematic Review. Clin Infect Dis. 2016;63(7):944–8.
15. Plassmann P, Monitoring chronic wounds and determining treatment. Farrar. D. UK: Advanced Wound Repair Therapies, Woodhead Publishing, 2011, pp. 130–152.
16. Tornow M, Kaszubiak J, Kuhn R, Michaelis B, Schindler T. Hardware Approach for Real Time Machine Stereo Vision. *Int J Syst Cybern Inform*. 2005;4.
17. Pena G, Kuang B, Szpak Z, Cowled P, Dawson J, Fitridge R. Evaluation of a Novel Three-Dimensional Wound Measurement Device for Assessment of Diabetic Foot Ulcers. *Adv Wound Caref*. 2020;9(11):623–31.
18. Pappachan JM, Cassidy B, Fernandez CJ, Chandrabalan V, Yap MH. The role of artificial intelligence technology in the care of diabetic foot ulcers: the past, the present, and the future. World J Diabetes. 2022;13(12):1131–9.
19. Nather A, Cao S, Chen JLW, Low AY. Prevention of diabetic foot complications. Singapore Med J. 2018;59(6):291–4.
20. Najafi B, Reeves ND, Armstrong DG. Leveraging smart technologies to improve the management of diabetic foot ulcers and extend ulcer-free days in remission. Diabetes Metab Res Rev. 2020: 36 Suppl 1, e3239.
21. Zhang X na, Ma Z jun, Wang Y, Sun B, Guo X, Pan C qing, et al. *Angelica Dahurica* ethanolic extract improves impaired wound healing by activating angiogenesis in diabetes. Caporali A, editor. PLoS ONE. 2017;12(5):e0177862.
22. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers: Diabetic foot ulcers. Ann NY Acad Sci. 2018;1411(1):153–65.
23. Tchanque-Fossuo CN, Ho D, Dahle SE, Koo E, Li C, Isseroff RR, et al. A systematic review of low-level light therapy for treatment of diabetic foot ulcer. Wound Rep and Reg. 2016;24(2):418–26.
24. Karkada G, Maiya GA, Arany P, Rao M, Adiga S, Kamath SU. Effect of Photobiomodulation Therapy on Oxidative Stress Markers in Healing Dynamics of Diabetic Neuropathic Wounds in Wistar Rats. Cell Biochem Biophys. 2022;80(1):151–60.
25. Wound Care Dressing – Maxiocel.: [cited 2022 August 16]. Available from: https://axiobio.com/maxiocel/wound-care-dressing/ [Website]
26. Maxiocel – 100% Chitosan Wound Dressing on Diabetic Foot Infection (Amputation).: [cited 2022 August 14]. Available from: https://axiobio.com/uploads/pdf/maxiocel/diabetic-foot-infection-amputation-case-study-6-maxiocel.pdf [Website]
27. Maxiocel – 100% Chitosan Wound Dressing on Diabetic Foot Infection (Amputation).: [cited 2022 August 14]. Available from: https://axiobio.com/uploads/pdf/maxiocel/diabetic-



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foot-infection-amputation-case-study-6-maxiocel.pdf [Website]

28. Heuch L, Streak Gomersall J. Effectiveness of offloading methods in preventing primary diabetic foot ulcers in adults with diabetes: a systematic review. JBI Database Syst Rev Implement. 2016;14(7):236–65.
29. Oguntibeju OO. Medicinal plants and their effects on diabetic wound healing. Vet World. 2019;12(5):653–63.
30. Jia H, Yang B, Li Y, Liang C, Lu H, Lin D, et al. Chinese medicine ulcer oil promotes the healing of diabetic foot ulcers. J Int Med Res. 2018;46(7):2679–86.
31. Sun Y, Lenon GB, Yang AWH. Phellodendri Cortex: A Phytochemical, Pharmacological, and Pharmacokinetic Review. Evid Based Complement Alternat Med. 2019;2019:1–45.
32. Xiong Y, Huang H, Li Y, Jiang G, Du L. Effect of Yinhuangsan (YHS) on Diabetic Foot Ulcers (DFU): A Systematic Review and Meta-Analysis. J Diabetes. 2021;11(03):97–114.
33. Liu Y, Li Y, Du Y, Huang T, Zhu C. Multicenter Clinical Trials Analyzing Efficacy and Safety of Topical Cortex Phellodendri Compound Fluid in Treatment of Diabetic Foot Ulcers. Med Sci Monit [Internet]. 2020 Jun 19 [cited 2023 May 20];26. Available from: https://www.medscimonit.com/abstract/index/idArt/923424 [Website]
34. Lee K, Shin MS, Ham I, Choi HY. Investigation of the mechanisms of *Angelica dahurica* root extract-induced vasorelaxation in isolated rat aortic rings. BMC Complement Altern Med. 2015;15(1):395.
35. Guo J, Hu Z, Yan F, Lei S, Li T, Li X, et al. Angelica dahurica promoted angiogenesis and accelerated wound healing in db/db mice via the HIF-1α/PDGF-β signaling pathway. Free Radic Biol Med. 2020;160:447–57.
36. Babu Natarajan S, Das SK, Chandran SP, Myo Oo A, Kanneppady SS, Entezarian M, et al. *Moringa oleifera* leaf extract loaded hydrogel for diabetic wound healing. Malaysian J Med Res. 2018;2(2):35–41.
37. Amali Muhammad A, Fakurazi S, Arulselvan P, See CP, Abas F. Evaluation of wound healing properties of bioactive aqueous fraction from *Moringa oleifera* Lam on experimentally induced diabetic animal model. Drug Des Devel Ther. 2016;1715.
38. Gupta R, Mathur M, Bajaj VK, Katariya P, Yadav S, Kamal R, et al. Evaluation of antidiabetic and antioxidant activity of *Moringa oleifera* in experimental diabetes: Antidiabetic activity of *M. oleifera*. J. Diabetes. 2012;4(2):164–71.
39. Kulkarni Y, Emmi S, Dongargaon T, Wali A. Wound healing effect of Vimlāpanakarma with Jātyādi tailam in diabetic foot. Ancient Sci Life. 2015;34(3):171.
40. Dhande P, Simpy R, Nargis I, Sanghavi D, Vijaya A. Burn wound healing potential of Jatyadi formulations in rats. Res J Pharm Biol Chem Sci. 2012;3:747–54.
41. Jose A, Adiga S, Ciraj A, Shettigar K, Velladath S, Ramachandra L. Management of grade IV diabetic foot ulcer by vrana ropana chikitsa: A case study. J Med Sci. 2021;0(0):0.
42. Lim JZM, Ng NSL, Thomas C. Prevention and treatment of diabetic foot ulcers. J R Soc Med. 2017;110(3):104–9.
43. Manning L, Hamilton EJ, Raby E, Norman PE, Davis W, Wood F, et al. Spray on skin for diabetic foot ulcers: an open label randomised controlled trial. J Foot Ankle Res. 2019;12(1):52.
44. Aerosol images.: [cited 22 August 2022]. Available from: https://www.pngwing.com/en/free-png-zeqnb [Website]
45. Pharmaceutical aerosol – uses and advantages.: [cited 2022 August 22]. Available from: http://pharmabiz.com/NewsDetails.aspx?aid=113171&sid=9 [Website]