

Polyherbal formulation: An alternative therapeutic approach to treat diabetic foot ulcer

Debasmita Dubey¹, Shakti Rath^{2,*}, Rajesh Kumar Meher³, Siba Prasad Dalai⁴, Jayant Kumar Dash⁵, Santosh Kumar Swain⁶

¹Medical Research Laboratory, IMS and SUM Hospital, Siksha 'O' Anusandhan Deemed to be University, Kalinga Nagar, Bhubaneswar, Odisha, India; ²Central Research Laboratory, Institute of Dental Sciences, Siksha 'O' Anusandhan Deemed to be University, Kalinga Nagar, Bhubaneswar, Odisha, India; ³Advanced Center for Treatment, Research & Education in Cancer, Tata Memorial Center, Mumbai, India; ⁴Department of Medicine, IMS and SUM Hospital, Siksha 'O' Anusandhan Deemed to be University, Kalinga Nagar, Bhubaneswar, Odisha, India; ⁵Department of Plastic, Reconstructive and Cosmetic Surgery, IMS and SUM Hospital, Siksha 'O' Anusandhan Deemed to be University, Kalinga Nagar, Bhubaneswar, Odisha, India; ⁶Department of Otorhinolaryngology, IMS and SUM Hospital, Siksha 'O' Anusandhan Deemed to be University, Kalinga Nagar, Bhubaneswar, Odisha, India

*Corresponding author: Shakti Rath, Central Research Laboratory, Institute of Dental Sciences, Siksha 'O' Anusandhan Deemed to be University, Kalinga Nagar, Odisha, India. E-mail: dr.shaktirath@gmail.com

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ABSTRACT

Diabetic Foot Ulcers (DFUs) are a common complication of poorly controlled diabetes and often become infected, termed diabetic foot infection. Despite using several multidisciplinary techniques, no significant cure is still achievable. So, it needs an alternative therapeutic approach to treat diabetic foot ulcers. So it needs to search for alternative highly effective nontoxic drugs or polyherbal formulations from plants to treat DFUs. In this study, we reviewed possible plants and research pathways that can be used to formulate an effective and safe herbal formulation to treat DFUs.

Keywords: Diabetic foot ulcers, alternative therapeutics, polyherbal formulations

INTRODUCTION

Diabetes is a metabolic disorder affecting human blood sugar level regulation,

leading to several systemic diseases and various other health complications leading to a shorter life expectancy.[1] As per the International Diabetes Federation (IDF),

nearly 400 million people worldwide have diabetes. India has the second-largest diabetic population with an estimated figure of 77 million, next to China. The increasing prevalence of diabetes has been mainly linked to population ageing and improper dietary habits; however, there has been a decrease in mortality rates due to improvements in diabetic treatment policy [2]. Diabetes prevalence among adults aged 20 to 79 was expected to be 10.5 % (536.6 million) in 2021, increasing to 12.2 % (783.2 million) in 2045. Men and women had equal rates of diabetes, with those aged 75–79 years old having the most excellent rates. Prevalence was expected to be greater in urban (12.1 %) than rural (8.3 %) regions in 2021 and high-income nations (11.1 %) than in low-income countries (5.5 %). Between 2021 and 2045, middle-income nations are anticipated to have the highest relative growth in diabetes prevalence (21.1 %), followed by high-income (12.2 %) and low-income (11.9 %) countries. In 2021, global diabetes-related health expenses were forecast to be USD 966 billion, and by 2045, they are expected to be USD 1054 billion [3].

Diabetic foot ulcer

Diabetic Foot Ulcers (DFUs) are significant comorbidities of diabetes

mellitus that warrant healthcare costs and may lead to death. DFUs afflict 19–34 % of diabetic individuals at some point in their lives, and the IDF estimates that 9.1–26.1 million people get DFUs each year.[4] Given that the clinical consequences of developing a DFU are not insignificant, these figures are concerning. According to population-based cohort research in the United Kingdom, the development of a DFU is linked to a 5 % death rate in the first 12 months and a 42 % mortality rate within five years.[5] DFU-positive patients were also discovered. Compared to people with diabetes without foot wounds, those with DFUs had a 2.5-fold greater mortality risk. Furthermore, patients with DFUs have a significant burden of healthcare interactions and high morbidity, inferior health-related quality of life, and poorer psychosocial adjustment [6].

Multidisciplinary diabetic foot care is rapidly becoming a staple of therapy to cure diabetic foot ulcers, including surgical debridement (Autolytic debridement with hydrogels, enzymatic debridement), wound dressing, vascular assessment, and treatment of active infection by using antibiotics, glycemic control, adjuvant therapy, biosurgery, hydrotherapy etc. Despite using these multidisciplinary

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techniques, no significant cure is still achievable. So, it needs an alternative therapeutic approach to treat diabetic foot ulcers [4-6].

DFUs are associated with both Gram-positive and harmful bacteria. Literature suggests that *Pseudomonas*, *E. coli* and *S. aureus* are the significant bacteria isolated from the diabetic foot. Since there is a lot of variation in the infection pattern of DFUs, pragmatic microbial identification and antibiotic sensitivity tests become essential to address this issue. Moreover, with the advent of multidrug resistance bacteria, the effectiveness of broad-spectrum antibiotics to treat DFUs has become an uphill task.[7] So, it becomes a primary concern to search for alternative highly effective nontoxic drugs or polyherbal formulations from plants to treat DFUs. Although a considerable amount of work has been reported on the development of an herbal formulation to treat DFUs, no serious attempt has been made to combat DFUs infected with MDR strains

Herbal formulations used against diabetic foot ulcer

Many types of plants and herbs with wound-healing properties have been found in Africa and other developing nations due to ethnobotanical surveys. The use of

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medicinal plants in wound treatment and care entails cleaning, debridement, and the creation of an appropriate environment for natural healing.[8] Ingredients from medical plants are thought to be less toxic. They have fewer side effects than standard therapeutic medicines, which explains the revived interest in using medicinal plants in wound healing, both in diabetes and non-diabetic situations. Impairment in diabetic wound healing is viewed as a severe health challenge by health professionals worldwide, and it is sometimes linked to non-specific aetiology. As a result, one of the therapeutic approaches for treatment is medicinal plants, especially in low-resource settings [9].

Viswanathan *et al.* evaluated the daily topical administration of a polyherbal formulation with silver sulfadiazine cream in 38 patients with DFUs in a single-centre, open-label, and phase III clinical research. *Glycyrrhiza glabra*, *Musa paradisiaca*, *Curcuma longa*, *Pandanus odoratissimus*, *Aloe vera*, and *Cocos nucifera* oil were used in the polyherbal cream, which all have antibacterial and anti-inflammatory effects. The off-loading procedure was employed in both groups, and dressings were changed every day with a thin layer of cream following irrigation with normal

saline. Both groups substantially reduced wound size at 5-month follow-up compared to baseline values. In both groups, the average healing period was 43 days, demonstrating that the polyherbal formulation is equally effective as the criteria standard (silver sulfadiazine cream) with no significant adverse effects [10].

The wound healing activity of a 3-mm-thick layer topical kiwifruit dressing combined with standard treatment (surgical debridement, ciprofloxacin 500 mg twice daily, and clindamycin 600 mg three times daily) was compared to routine care in 37 patients with DFUs in a randomised, controlled clinical trial. Following usual therapy, the treatment group received kiwifruit dressing twice daily. Compared to the control group, the intervention group's ulcer size and time to wound closure were significantly reduced after 21 days of therapy.[11]

To explore the effectiveness and tolerability of *Ageratina pichinchensis* as a topical wound healing agent, Romero-Cerecero et al. undertook randomised, double-blind, controlled pilot research with 30 patients with DFUs. Patients in the trial got a 5 per cent cream formulation of n-hexane/ethyl acetate extract of *A. pichinchensis*. In contrast, the control

group received 1 per cent micronised silver sulfadiazine once a week. Wound healing had occurred in 77.5 % of the patients in the intervention group after six weeks, compared to 69.8 % of the patients in the control group. The average time to wound healing for the intervention group was 65 days, whereas the control group took 77 days [12].

Soleimani et al. evaluated the impact of supplementary flaxseed oil omega-3 fatty acids in 60 patients with Wagner grade 3 DFUs in a randomised, double-blind, placebo-controlled clinical experiment. The supplement was taken orally twice a day in 1000 mg capsules. Flaxseed oil reduced ulcer size, serum insulin concentration ($p = .002$), haemoglobin level ($p = .01$), and serum high-sensitivity C-reactive protein level ($p = .01$) after 12 weeks of therapy. Furthermore, the quantitative insulin sensitivity checks score ($p = .002$), plasma total antioxidant capacity ($p = .001$), and glutathione concentrations ($p = .03$) all showed substantial improvements. These findings suggest that this supplement aids wound healing by improving the metabolic profile of diabetic individuals.[13]

Masoompour et al. observed that daily intravenous infusion of Product A

significantly impacted wound size reduction compared to baseline values ($p = .009$) in a non-controlled clinical study including ten patients with DFUs. Another clinical research with a randomised, controlled, the multicenter design was conducted to corroborate the findings of this study, in which the wound healing effects of Product A were compared to conventional treatment. Once a day, 4 mL of Product A was diluted in 50 mL to 100 mL of normal saline and administered over 1 hour in the intervention group. The control and intervention groups were given standard treatment, such as wound dressing, debridement, and systemic antibiotics. The intervention group substantially decreased wound surface area after four weeks of therapy compared to baseline data ($p = 0.000$). Furthermore, patients in the intervention group had a wound closure rate of 64 %, compared to 25 % in the control group ($p = 0.0001$). [14] Refined olive oil was evaluated in a randomised, double-blind clinical investigation, including 30 individuals with DFUs. A daily application of olive oil was used in conjunction with conventional therapy for four weeks, and the outcomes were compared to those of a control group that received just traditional treatment.

Compared to traditional therapy alone, using olive oil + traditional medicine reduced wound size ($p = .01$) and depth ($p = .02$). Furthermore, 73.3 % of patients treated with olive oil had wholly healed wounds, compared to just 13.3 % in the control group ($p = .003$). It should be emphasised that because polyphenolic chemicals have potent antioxidant activity and are abundant in extra-virgin olive oil, future studies on this form of olive oil may be worthwhile [15].

The oral consumption of *Tinospora cordifolia* aqueous extract significantly reduced the frequency of surgical debridements in patients with DFUs in a randomised, double-blind, placebo-controlled clinical study including 45 patients ($p = .03$). However, there were no statistically significant impacts on ulcer size and depth, neutrophil count, or bacterial clearance. It was claimed that polymorphonuclear cells' increased phagocytic activity acted as a regulator to promote wound healing. However, this study does not indicate the supplement's dose, and more research into the plant's safety and efficacy are needed [16].

Leung *et al.* evaluated the safety and effectiveness of an oral polyherbal formulation in 80 patients with DFUs in

randomised, placebo-controlled clinical studies. In equal quantities, the herbal formula included *Radix astragali*, *Radix Rehmannia*, *Rhizoma Atractylodis Macrocephalae*, *Radix Stephaniae Tetrandrae*, *Radix Polygoni Multiflori Preparata*, *Rhizoma Smilacis Chinensis*, *Poria Rhizoma Dioscoreae*, *Fructus Schisandrae Chinensis*, *Cortex Mout*. The patients were given enough anti-diabetic and antibacterial drugs and daily dressings and cleanings with 1 % chlorhexidine gluconate solution. The herbal drink mixture was given orally twice a day to participants in the treatment group for four weeks, while the control group got a placebo. TNF levels had fallen considerably in the intervention group given the polyherbal preparation compared to the control group by the end of week four (42 % and 10 %, respectively; $p = .037$), indicating the supplement's considerable anti-inflammatory capabilities. Furthermore, when compared to baseline values, surface oxygen tension was considerably improved in the intervention group ($p = .005$); however, there was no significant improvement in the placebo group ($p = .76$). 41 In the intervention group, wound healing was seen to be quick [17].

The efficacy and safety of Tangzu Yuyang Ointment (Product B), a topical Chinese herbal preparation, were compared to standard wound therapy, which included local debridement, off-loading, and dressings in a prospective, randomised, controlled, and add-on clinical trial conducted in seven Chinese centres. Product B contains the roots of *Coptis Chinensis* Franch, *Ligusticum chuanxiong* Hort, *Atractylodes lancea* (Thunb.) DC, *Panax notoginseng* (Burk.) F.H Chen, *Angelica sinensis* (Oliv.) Diels, *Arnebia euchromatin* (Royle) Johnst, *Rheum officinale* Baill, *Phellodendron* (calcium sulfate) [18].

Sesame oil and beeswax were the foundation for the formulation, made in a bacteria-free environment. This study included a total of 48 participants with DFUs. Nine patients were never followed. Standard wound care (saline gauze) was given to the treatment group, as well as a 1-mm-thick coating of Product B was applied to the ulcer surface. Patients in the control group, on the other hand, got just primary wound care. The healing rate in the intervention group was considerably more significant than in the control group after 24 weeks (91.7 % vs 62.5 %, respectively; $p = .036$) [19].

Kuo *et al.* compared the efficacy and safety of an herbal cream to hydrocolloid fibre wound dressing (a common DFU therapy approach) in 21 patients in a randomised, single-centre, controlled, open-label clinical experiment. Three patients were never followed. On an essential cream basis, the 1.25 % cream was made from the most active fractions of *Plectranthus amboinicus* (Lour.) Spreng. And *Centella asiatica* (L.) Urban in a 1:4 ratio. The intervention group applied the herbal cream to the wound site in a 2-mm thick layer twice a day for two weeks. A hydrocolloid fibre dressing was administered once a week in the control group. There was no significant difference in wound size between the two groups at the 2-week follow-up. This demonstrates that the herbal cream is just as effective as the conventional medication. Although wounds treated with the herbal cream showed a more significant improvement in the Wagner grade, the difference was not statistically significant. Compared to other clinical trials on DFUs, the treatment time in this research was very short (2 weeks). Hence additional studies with more extended follow-up periods are needed to

properly establish the impact of this herbal preparation on conventional therapy.[20]

Traditional Chinese Medicine (TCM) had a variety of degrees and paths of action in the healing of diabetic wounds. Additional research on precision-targeted therapy offers suggestions for examining the primary target of TCM in treating diabetic wounds and developing cutting-edge, contemporary medications based on this target [21-23] Various literature suggests that combinations of several plants (Table 1) are used as a treatment of DFUs both in traditional and complementary medicine system like Unani, Ayurveda, traditional Indonesian and African medicinal system [24-28].

Proposed hypothesis

Being unique and composed, phytochemicals become a vital tool to fight MDR microorganisms [29,30]. Figure 1 gives a possible research pathway that includes both in-vitro and in vivo methods that can be considered for developing a safe and effective herbal formulation that can be used to treat DFU.

Table 1. Plants used in traditional and complementary medicinal systems to treat DFUs

Plants	Parts used
<i>Acacia nilotica</i>	Leaf
<i>Acalypha langiana</i>	Entire herb
<i>Aloe vera</i>	Leaf
<i>Annona squamosa</i>	Leaves and seeds
<i>Anogeissus leiocarpus</i>	Bark and roots
<i>Areca catechu</i>	Seeds
<i>Balanite aegyptiaca</i>	Fruit and Seed Aqueous
<i>Carica papaya</i>	Fruits
<i>Catharanthus roseus</i>	Leafs and Flower
<i>Centella asiatica</i>	Entire herb
<i>Commiphora molmol</i>	Essential oils
<i>Curcuma longa</i>	Rhizome
<i>Eleutherine americana</i>	Bulbs
<i>Ficus glumosa</i>	Leaf
<i>Garcinia mangostana</i>	Fruit and pericarp
<i>Guiera senegalensis</i>	Leaves and roots
<i>Hylocereus undatus</i>	Leafs and Flower
<i>Lawsonia inermis</i>	Leaves
<i>Martynia annua</i>	Entire herb
<i>Nigellia Sativa</i>	Seeds and oils
<i>Orthosiphon aristatus</i>	Leaves
<i>Piper nigrum</i>	Leaf and essential oil
<i>Punica granatum</i>	Flowers and fruits
<i>Radix Rehmanniae</i>	Tuberous root
<i>Rosmarinus officinalis</i>	Leaves
<i>Rubia cordifolia</i>	Root
<i>Senna alata</i>	Leaf
<i>Zingiber cassumunar</i>	Rhizome
<i>Zingiber officinale</i>	Rhizome

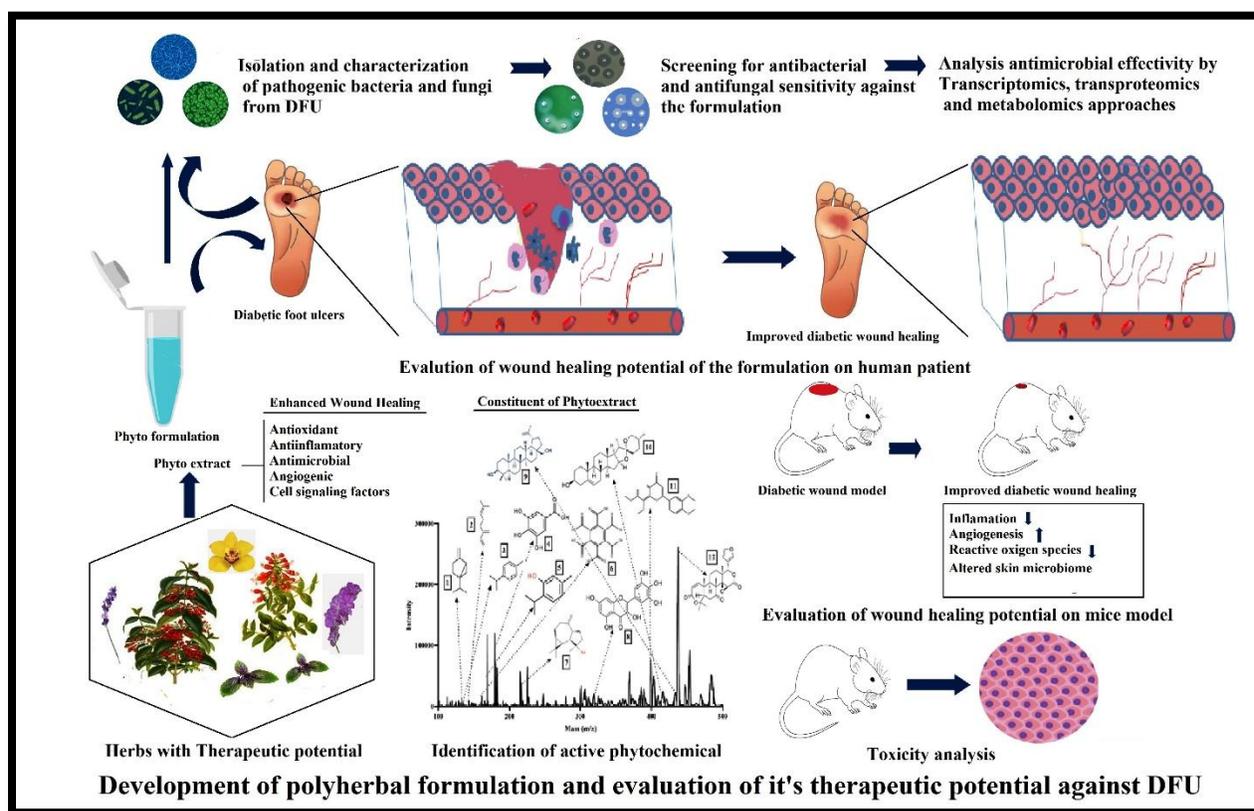


Figure 1. Development of polyherbal formulation and evaluation of its therapeutic potential against DFU.

CONCLUSION

Several herbal products have been used to treat diabetes and DFUs that lack proper scientific. Since plants and their concentrates include different unique metabolites, the synergistic effect of different phytochemicals can also be used to treat DFUs. However, rigorous research

is required to validate the efficacy and safety before they can be used on a large scale. As diabetes is growing throughout the world, the incidences of DFUs is also increasing. Hence, an effective and safe polyherbal compound is the need of the hour to deal with this problem.

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