Herbal Medicine and the Diabetic Foot Ulcer

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Abstract

The purpose of this paper is to identify medicinal herbs that can effectively treat diabetic ulcers and be included in a topical formula. Diabetic foot ulcers (DFU) are a complication of diabetes mellitus (DM) that have high-risk mortality and morbidity (Kumar et al., 2023). Diabetic wounds are highly resistant to healing and fail to progress normally through the four stages of wound healing. Of the approximately five hundred and thirty-six million persons with diabetes in 2021, up to 34% will experience diabetic foot ulcers during their lifetime (Monaghan et al., 2023). Death and lower limb amputations occur in 32% of persons with diabetic foot ulcers, and less than half of diabetic foot ulcers heal within the first year, with many recurring later (Kumar et al., 2023).

Several medicinal plants have the potential to aid and increase wound healing rates, re-epithelization, modify growth factors, reduce bacterial and microbial infections, and increase angiogenesis. *Lavandula angustifolia*, *Calendula officinalis*, *Rosmarinus officinalis*, *Plantago major*, *Aloe vera*, *Eucalyptus alba, Azadirachta indica, Hypericum perforatum, Resina draconis, Commiphora myrrha,* and olive oil are all discussed in this literature review and every one of these herbs was shown to have positive effects in diabetic wound healing. *Lavandula angustifolia* significantly impacted all stages of wound healing and antimicrobial effects. Olive oil also emerged as having significant importance in diabetic wound healing, mainly because of the ease of access from local retailers and its ability to create a moist healing environment (Abdoli et al., 2022). *Aloe vera* was remarkable for its effects on matrix metalloproteinase and *Azadirachta indica* for inhibiting anti-methicillin-resistant Staphylococcus aureus. *Calendula*

officinalis, Hypericum perforatum, and *Plantago major* aided in wound healing, increased wound closure rates, effects on collagen synthesis, and increased wound tensile strength. This literature review proves medicinal plants' significant role in diabetic wound healing. It gives crucial information for creating a diabetic wound formula that targets all four stages of wound healing.

Introduction

Diabetic foot ulcers (DFU) are a complication of diabetes mellitus (DM) that have high-risk mortality and morbidity (Kumar et al., 2023). Five hundred and thirty-six million persons had diabetes in 2021, and this number is expected to rise to 783 million by 2045 (Monaghan et al., 2023). Of this number of people, approximately 19-34% experience diabetic foot ulcers during their lifetime. The primary issue with DFUs is that they do not heal per normal expectations. Statistically, only 46% of DFUs heal within the first year, 10% recur, and 32% die from complications or have a lower limb amputated (Kumar et al., 2023).

There are many reasons why DFU do not heal, mainly neuropathy, reduced levels of endogenous growth factors, decreased collagen production, impaired angiogenesis, prevention of clot formation, impaired re-epithelialization, the decreased production of extracellular matrix, and prolonged inflammation response. Damaged blood arteries are a primary factor in the delay of healing. This leads to the hypoxia-inducible factor (loss of oxygen) that restricts the production of vascular endothelial growth factors needed to regenerate blood vessels. Neuropathy, damage to the nervous tissue due to abnormal blood flow, can result in a loss of feeling in the extremities and can be a primary reason why persons with DM do not notice ulcers or feel pain (Monaghan et al., 2023). Decreasing prolonged inflammation is the primary target of DFU care. If inflammation is reduced, the normal body functions of repair can begin.

However, in DFU, this does not occur, and many persons never progress into the four phases of wound healing. These phases are hemostasis or clotting, which is impaired due to blood vessel damage and neuropathy; inflammation, which is continuous and exaggerated;

proliferation, which is delayed or entirely disrupted; and remodeling, which is the process of re-epithelialization or the rebuilding of tissue (Akbik et al., 2006). The first phase, hemostasis, occurs immediately upon injury and is essential for cell migration to the injury site. The second phase, inflammation, occurs almost simultaneously when the cells migrate to the site. These cells include phagocytes, neutrophils, and macrophages. Phagocytes are essential; they begin cleaning up and removing foreign debris. Neutrophils are one of the first responders to the site of a wound and play a vital role in the inflammation stage (Ma et al., 2023). Neutrophils are responsible for the secretion of cytokines that both encourage fibroblast migration and increase inflammation (Akbik et al., 2006; Ma et al., 2023). Neutrophils release both matrix metalloproteinases and vascular endothelial growth factor (VEGF) and expel extracellular traps (NETs) (Ma et al., 2023). All of these are important during the inflammation phase, but prolonged secretion inhibits later stages of wound healing. Elevated blood glucose levels in diabetic patients have been shown to increase the levels of NETs secreted by neutrophils. They are believed to be a primary cause of delayed wound healing.

In typical wound healing, the inflammation stage leads to the proliferation phase. However, this stage is prolonged in diabetic wounds. Fibroblast migration signaled by neutrophils leads toward the end of the inflammation phase in routine wound healing. The migration of fibroblasts is often delayed or absent in diabetic wounds, preventing re-epithelization. This is critical as fibroblasts are responsible for secreting the extracellular matrix (ECM) in which new cell growth takes place, and the promotion of fibroblast proliferation is a primary focus of diabetic wound healing and herbal medicine.

Any treatment aims to prevent or treat infection, reduce inflammation, and encourage new tissue growth. Herbal medicine can play a significant role in encouraging all of these phases. This paper aims to evaluate herbs that are clinically proven effective for diabetic wound healing and explore herbs that have potential for use on DFUs. Currently, there is no standard herbal formulation that provides healing to DFU. The primary goal of this research is to identify herbs that may be useful in herbal preparation for use on diabetic wounds.

Elimination of bacterial infection is of first importance, and treatment of the five microorganisms that have been identified in DFUs, *E. coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Streptococcus pyrogens,* can be accomplished with several plants (Kumar et al., 2023). Azadirachta indica, or neem oil, has been proven effective as an antimicrobial for *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Villani et al., 2024). Neem has also shown an anti-inflammatory capacity for use as an irrigation agent for DFU and to help in the formation of collagen and new capillaries (Jayalakshmi, M., 2020; Banerjee et al., 2020; Chundran et al., 2015). Al well-known her St. John's wort Hypericum perforatum has proven to reduce inflammation, speed wound healing time, increase tissue regeneration, and aid in revascularization and re-epithelialization (El-Elimat et al., 2023; Yadollah-Damavandi et al., 2015; Pesin Suntar et al., 2009; Altiparmak et al.; T., 2018). St. John's is practical and gentle, as clinical trials have shown it is applicable for post-partum healing of perineal wounds (Yahya et al., Z., 2020). Further reduction of inflammation can be accomplished by using other anti-inflammatory herbs, such as lavender essential oil, which has been clinically shown to reduce inflammation through several pathways and to aid in chronic wound healing (Ao et al., 2023).

Calendula officinalis, *Rosmarinus officinalis*, *Plantago major*, *Aloe vera*, and olive oil have all been shown to aid in wound healing and reduce inflammation.

Lastly, in the encouragement of new tissue growth, *Eucalyptus alba* effectively stimulated cell growth in rat models and has significant promise in DFU healing (Mumtaz, R., 2022). *Resina draconis* or dragon's blood as it is commonly known, has also shown promise in speeding up the rate of healing of DFU (Feng et. al., 2021). Myrrh, *Commiphora myrrha*, is shown to aid in collagen fiber remodeling and has been used since ancient times in China for wound healing (Bahjet et al., 2019). Myrrh has also been studied in combination with honey and bee propolis for healing infected wounds (Lotfy et al., 2006). Honey has been studied in other clinical trials and is an effective remedy for DFU when combined with other constituents (Faraji et al., 2023). Curcumin extracted from turmeric is of particular significance for its ability to promote angiogenesis and the regulation of specific growth factors (Kant et al., 2015).

Methods

A review of medical journals and clinical trials on diabetic ulcers and wound healing was conducted to locate plant-based medicinal herbs for use in diabetic wound healing. Primary research was conducted on the EBSCO database. Keywords used in all searches included diabetic ulcers, diabetic wounds, or diabetic sores in combination with herbal medicine, herbal, and complementary and alternative medicine (CAM). Articles containing nonherbal or plant-based, multi-herb, no-topical preparations such as oral preparations for irrigation use, nanotechnology, Chinese medicine preparations, stem cells, injectables, drug delivery systems, and genetically modified ingredients were excluded. The exclusion of Chinese medicine preparations was due to limited access to the plants in the United States. All other exclusions

were due to their lack of relevance to the research topic. All the individual herbs in these studies were further evaluated for additional clinical trials using the following search criteria: diabetic ulcers + herb name and wound healing + herb name.

The Natural Medicines Database was used to source individual herbs not previously found using the "Comparative Effectiveness" database listing all the natural substances with effectiveness ratings. The efficacy chart for "diabetic foot ulcers" was used as a source of potential herbs. All listed herbs were included, and studies were removed if they were orally conducted, mixed plant studies without any direct mechanism of action to one single plant, or the studies were already obtained in prior searches.

In total, 79 articles were identified and evaluated for their potential use as an herbal component in a topical remedy for diabetic ulcers. To reduce the number of studies included in this paper, herbs that had only one clinical study were eliminated. Studies about episiotomy or cesarean trials were also eliminated, and studies in which the full text could not be obtained or was not in English were removed.

Results

Several plant-based preparations have been studied to determine their ability to promote increased healing rates in diabetic wounds. Several essential factors emerge in determining an herb's potential in wound healing. These are the rates of wound closures, inflammation reduction, angiogenesis promotion, and the effects on growth factors and wound healing processes. Predominantly, these studies utilize rat models by inducing diabetes and wound creation. These studies provide critical information that led to the efficacy of trials on humans. Human trials are limited and involve other forms of treatment, such as antibiotic use,

debridement, and the use of saline to cleanse the wounds. Animal models can demonstrate the potential of a preparation without the need for other interventions.

Wound Closure Rates

The rate of closure of diabetic wounds is significantly reduced with the use of medicinal herbs as compared to controls. Studies show that several herbs have a positive effect on increasing the rate of wound closure. While mechanisms of action are not identified in all studies, the potential use of the herb for diabetic wounds is still demonstrated. The use of measurements to determine the closure rate is comparable in all of the studies, and statistical analysis was typically performed using S.P.S.S. software in the more significant portion of the studies. While all studies measured wound closure rates, other studies examined tissue samples to determine the type of tissue present.

Plantago

An open-label randomized controlled trial was conducted on 120 participants with diabetic foot ulcers and pressure ulcers. The participants were divided into treatment and control groups (Ghanadian et al., 2022). Twenty-six participants did not complete the study due to lack of follow-up, early discharge, or death. The treatment group received a gel extract of 10% *Plantago major* and instructions on cleaning the wounds with saline solution and applying sterile gauze dressings and bandages daily. The control group received a standard of care wound dressing that varied depending on the severity of the wound, including topical applications of either alginates, honey, hydrocolloids, hydrogels, and silver-containing dressings. All dressings were applied once daily for two weeks. Surgical debridement and antibiotics were administered

to both groups as deemed necessary. The primary measurement of this study was overall wound size, with cases of erythema around the area of the wound and complete wound healing being secondary outcomes of the study. Both groups had a reduced wound size, with the Plantago group having an overall more significant reduction in wound size by week two. Complete wound healing was more significant in the treatment group versus the control group, 64% and 20.5%, respectively. Additionally, rates of erythema were significantly lower in the treatment group during the second week of the study.

Calendula

Calendula is known for its wound-healing properties and has been used to treat skin infections and burns (Ulbricht, C., 2010). Calendula prevents skin dermatitis in breast cancer patients undergoing radiation therapy and can reduce the area's redness, irritation, and pain. To determine the use of calendula in treating diabetic wounds, researchers evaluated long-term topical treatment with *Calendula offici*nalis over 30 months in eighty-four persons (Buzz et al., 2016). Forty-three persons withdrew before the completion of the study due in large part to the failure to follow up and attend scheduled visits. Of the forty-one participants who completed the study, 68% had complete recovery after twenty weeks, an additional 10% of wounds wholly healed at 30 weeks, and the remaining 22% had an overall reduction of total wound area by 75%. Ulcer infection and inflammation rates were significantly decreased, with the calendula extract being effective against all identified strains of pathogens. There was no control group in this study, and it is not clear whether participants engaged in other treatments for their diabetic wounds during the 30-week treatment period. Researchers contributed the healing properties of calendula with the triterpene and flavonoid content.

A small cohort of 17 participants with injuries to the hand and fingers that were candidates for healing by secondary intention was chosen to participate in a study to determine if a standardized extract of *Calendula officinalis* was more effective at promoting healing than the standard treatment with mineral oil (Giostri et al., 2022). Both groups were instructed on how to clean and dress the wounds and apply the topical treatment twice daily. Participants were followed until complete epithelization was achieved. Daily imaging of wounds was taken, and the primary measurement was of wound healing time characterized by the appearance of the wound and lack of granulation tissue. Based on the univariate linear regression model, the treatment group had faster healing rates than the control group at 3.33 percentage points per day. The treatment group's average healing time was seven days compared to 11 days in the control group. The maximum healing time in the treatment group was 13 days compared to 21 days in the control group. The cohort was small due to the compliance and continuation of over half of the participants.

Rosemary

The potential of rosemary *Rosmarinus officinalis* as a healing agent for diabetic wounds was evaluated using the essential oil extracted from the aerial parts of the plant (Abu-Al-Basal, M., 2010). Diabetic-induced rats were wounded and divided into four groups. Group 1 consisted of non-diabetic rats who had received no treatment for their wounds. Group 2 diabetic mice that received a control injection of distilled water. Group 3 diabetic mice were injected with an aqueous extract of 10% rosemary. Group 4 diabetic mice were treated with a topical application of rosemary essential oil (REO) twice a day for three days. On day three, there was a significant increase in the formation of granulation tissue in the mice treated with topical REO compared to

the non-diabetic rats in group 1. Both groups 3 and 4 of the rosemary treatment groups showed a significant increase in granulation tissue formation and wound contraction compared to the untreated diabetic group. By day six, groups 3 and 4 showed increased wound closure rates compared to the non-diabetic control. On day six, all groups showed an increase in epithelialization compared to the untreated diabetic control group in group 2, with group 3 having the most significant rate of epithelization. Group 2, the untreated diabetic mice, had delayed coagulation, a marked increase in inflammation, poor granulation tissue formation, high levels of neutrophils, and very little fibroblast and extracellular matrix (ECM) presence. Both treatment groups and the non-diabetic control group had significant levels of ECM, very few neutrophils, and the formation of new blood vessels.

Pressure ulcers are similar to diabetic ulcers in several ways, as they have delayed healing and high rates of infections (Parizi et al., 2022). In this study, 70 patients with grade 1 pressure ulcers were treated with rosemary ointment after being washed with saline solution, and then sterile gauze was applied over the wound once a day for seven days. The control group received only standard care, such as daily washing with a saline solution and regular position changes. The study used qualitative data from ten experts and the Pressure Ulcer Scale for Healing Tool to evaluate wound healing. The experts gathered wound scores, and the inter-rater Kappa used was 0.9 to determine a high degree of agreement between the examiners. No significant difference between the two groups was observed on day 3. Significant differences were observed in the treatment group by day four, and wound healing was most pronounced on day 7. No side effects were observed, and researchers concluded that rosemary was a safe and effective treatment for grade 1 pressure ulcers.

Though not explicitly studied for diabetic ulcers, *Candida albicans* frequently infect open wounds of the skin (Nejati et al., 2015). *C. albicans* is usually present on the surface of the skin and the mucous membranes and is a significant risk factor for death in immunosuppressive patients with open wounds. *C. albicans* has become resistant to synthetic drugs, and herbal alternatives provide a novel approach to treatment. Rosemary is known to be antimicrobial and antioxidant, and other studies have shown it to be effective in treating other pathogens. Wistar rats were used for this experiment, and wounds were infected with *C. albicans* by injection. The rats were separated into a control group, a 2% treatment group, and a 4% treatment group. All treatments were performed for twenty days, and biopsies were taken every four days. The 2% and 4% treatment groups showed a significant decrease in yeast count compared to the control group, though it was not eliminated. The 4% treatment group showed the most significant rate of wound closure with complete healing at day 16. Histological tests of the treatment groups showed a significant increase in the total number of macrophages, fibroblasts, and collagen deposits and the development of new blood vessels.

Eucalyptus

Oxidative stress is caused by reactive oxygen species released by neutrophils in the initial inflammatory stage of wound healing (Ma et al., 2023). *Eucalyptus alba* is known to possess antioxidant and antimicrobial properties and has been used to treat infections and inflammation of wounds (Mumtaz et al., 2022). The polyphenols quercetin, rutin, and ellagic acid are among the constituents of eucalyptus and are known to have antioxidant properties and pharmacological activity. The in vitro study assessed the wound-healing potential of eucalyptus through the scratch wound healing assay, α-glucosidase inhibition assay, and the DPPH assay. The DPPH

assay evaluates the in vitro potential of a material for antioxidant activity, and the α-glucosidase inhibition assay for antidiabetic activity. The results of the DPPH assay showed potent effects, with the ethanol-based extract dried at 10° having the highest results. The α-glucosidase inhibition assay was dose-dependent and showed inhibition of α-glucosidase at 0.1mg/mL, with the highest antidiabetic activity in leaves dried at 30°C and extracted in ethanol. Wound healing activity showed similar results, with the most significant cell proliferation in the samples dried at 10° and 30°C. This study supports the potential for using eucalyptus in diabetic wound healing with the optimal extract obtained from leaves dried at 10° and extracted in ethanol.

One in vivo study examined the potential of eucalyptus, rosemary, and lavender for wound healing in rats infected with *Candida albicans* (El-Sakhawy et al., 2023). This study is briefly included as all of the herbs used in this preparation are included in this report, and the subject of *C. albicans* is discussed previously in the section on rosemary. The in vivo results of this study showed potent inhibitory effects of the three compounds against *C. albicans*. The extract of all three herbs also improved wound contraction and epithelization rates in rats and was superior to eucalyptus extract alone. The most significant results came from a 10% cream, which showed significant results in a reduction of fungal load and overall wound healing.

Olive Oil

Olive oil has been studied for use with other agents and in special preparations (Abdoli et al., 2022). In this study, the researcher looked at the potential of extra virgin olive oil to aid in healing diabetic foot ulcers. The olive oil was used with no other agents or herbs and was in a form that was commercially available at a local grocery store. Sixty persons with type 2 diabetes mellitus (T2DM) were enrolled in this assessor-blind randomized controlled study. Participants

were divided into treatment and control groups with no different demographic or anthropometric features and similar clinical factors associated with T2DM. Both groups were evaluated by a physician using Wagner's classification scale for wound grade. Assessments were conducted to evaluate the duration of wounds, the size and site, the status of vascular insufficiency, neuropathy, and any additional complications.

Measurements were taken to determine the surface area of wounds and the total depth of the ulcer(s). All participants received the same education on managing diabetic ulcers, irrigating with saline solution, cleaning and dressing the wounds, and being prescribed oral antibiotics. The treatment group was given additional instructions on the daily application of olive oil to the wounds prior to applying the dressings. The control group applied no additional substance to the wounds prior to dressing. Daily phone calls and weekly assessments by the same physician were conducted to monitor participants, and images were taken with a digital camera by participants. After four weeks of treatment, both groups reported improved overall ulcer status. However, the control group had significantly higher rates of healing. 76.6% of the participants in the intervention group observed complete healing of the wounds, while 0% of the control group had complete healing. None of the intervention groups had unhealed wounds, and 6.7% of the control group had no improvement. The remainder of both groups had partial healing. This study demonstrated that olive oil is an effective treatment for diabetic ulcers in conjunction with proper wound care and washing. Researchers contribute this to olive oil's ability to reduce inflammation, increase blood flow, and reduce oxidative stress. Olive oil's essential fatty acid content is believed to aid in cell healing, provide an antimicrobial environment, and prevent further infection of the area.

Inflammation, Growth Factors, and Expression Pathways

The following studies continued to look at wound closure rates and inflammation markers. These studies also looked at tissue samples for signs of collagen growth and angiogenesis and to check for specific growth factors. These studies provide critical information about each herb's potential mechanism of action and give a closer look at the stages of wound healing. Wound samples were used throughout the studies to help identify what is happening under the skin's surface. This is vitally important as several key factors have been identified in diabetic wounds, and knowing the herb's potential to act upon different phases of the wound healing process will help to develop a topical formula that addresses every stage of wound healing.

Olive Oil and Aloe Vera

The combination of *Aloe vera* and olive oil was evaluated in this study for treating chronic wounds and included 13 persons with diabetic ulcers, 41 persons with pressure ulcers, and six persons with venous ulcers (Panahi et al., 2015). Participants were divided into two groups: an *Aloe vera* and olive oil group (AVO) and a phenytoin cream group, which served as the control. The *Aloe vera* to olive oil ratio was 3:2 and contained no other ingredients. Both groups applied the creams twice a day for 30 days. The study measured outcomes based on initial baseline scores using the Bates-Jensen scales and a visual analog scale for pain severity. Both groups showed overall improvement, but the AVO group showed a marked improvement in overall wound size and depth, the amount and type of necrotic tissue, and the state of surrounding tissues. Both groups saw a reduction in overall pain, with the AVO group showing

the most significant reduction. Researchers attributed the effectiveness of the AVO cream over the phenytoin cream to olive oil's ability to decrease arachidonic acid synthesis and increase nitric oxide synthesis. *Aloe vera* contributed to the overall healing of the wounds by facilitating the production of type 1 collagen growth, keratinocyte growth factor, and endothelial growth factor. Researchers also believed that *Aloe vera* could heal a wide range of wounds of differing types.

Researchers in another olive oil and aloe trial utilized diabetic-induced male rats tested for diabetes based on blood glucose levels (Massoud et al., 2022). The benefit of using rats is that wounds in the control group can be left untreated, allowing for a clear delineation between treatment and non-treatment. The rats were shaved, and a 10mm wound area was made to test the difference between three topical preparations of plain herbs and an untreated control. The first preparation was of only *Aloe vera* gel, the second only olive oil, and the third a combination of both (AVO). The control group received no treatment for their wounds. The wound-closure rate was used as the primary identifier, along with tissue collection sample analysis for inflammation (NF-kB), cell proliferation (Ki-67), and angiogenesis (CD34). During days 0 through 7, there was no significant difference in wound healing rate between the four groups. Differences started to emerge on day nine, and by day 14, the AVO group wounds were almost completely healed while the other groups were still in earlier stages of healing. The AVO group had the most marked progress with a nearly complete loss of wound scab and growth of hair follicles and sebaceous glands. Immunohistochemical analysis of tissue samples revealed that the most significant expression of the cell proliferation marker was in the AVO group, as well as an increase in angiogenesis and functional vascular systems.

Aloe vera

Researchers at the Universitas Jenderal Soedirman in Indonesia evaluated the difference in the rate of diabetic foot ulcer healing between dressings containing *Aloe vera* and dressing soaked in saline solution (Aqsa et al., n.d.). Sixty participants were divided into two groups, with no statistical differences between the two groups. The study was conducted over eight days, and participants were evaluated on days one and eight. The study reported a statistically significant difference between the two groups, with the Aloe vera group having a greater rate of improvement. The marker of improvement was the formation of granulation tissue, with 100% of the Aloe vera group showing the formation of granulation tissue and only 53.3% of the control group showing improved formation. This study followed participants once the wounds were completely healed.

Aloe and MMP-9

Matrix metalloproteinase (MMP)-9 are zinc endopeptidases that degrade the extracellular matrix (ECM) and play a vital role in diabetic wound healing (Junren Chen et al., 2022). Overexpression on MMP-9 can lead to excessive degradation of the ECM and delay wound healing. Matrix metalloproteinase is an essential factor in diabetic wound healing as people with diabetes frequently have elevated levels of MMP-9, causing a lack of collagen formation and a failure of wounds to heal (Yunita et al., 2018). MMP-9 is essential in the early stages of wound healing as it cleans debris and bacteria. Tissue inhibitors of metalloproteinase normally regulate this process. However, diabetic wounds display a disbalance of these factors.

In order to investigate the potential of *Aloe vera* in regulating MMP-9, this study utilized diabetic-induced rats that were divided into two groups: an *Aloe vera* group and a control group.

Both groups had the wounds covered by a parafilm and gauze dressing, but only the Aloe vera group had any topical applied to the wounds. Immunohistochemistry analysis was used to determine the levels of MMP-9 on day twelve. The results showed a marked decrease in MMP-9 positive cells in the Aloe vera group compared to the control using the HSCORE formula. This demonstrates the ability of Aloe vera to modulate MMP-9 in the wound healing process and gives rise to the mechanism in which Aloe vera gel works in diabetic wound healing. The aloe group had several markers of wound healing throughout the twelve-day trial that were significantly improved over the control group, including the production of granulation tissue, reduction in necrotic tissue, increase in fibroblast tissue, and clear exudate from the wound versus the presence of purulent exudate from the control group.

Dragon's Blood, Dracorhodin perchlorate

TLR4 is an essential pathway in the regulation of inflammation and expression of cytokines IL-1β and TNF-α, along with COX-2 and iNOS. Both IL-1β and TNF-α cytokines are present at wound locations and can reduce the rate of wound healing (Xiong et al., 2022). TNF-α, in particular, can cause excessive damage to tissue if not adequately regulated by increasing the presence of neutrophils at a wound site. COX-2 and iNOS increase the inflammation response, and COX-2 further delays wound healing by decreasing the collagen creation process. Dragon's blood *Resina draconis* is used in Chinese medicine to promote and regulate blood circulation and is derived from the resin of the Kylin tree. Drachorhodin is a flavonoid extract of dragon's blood and is believed to promote certain growth factors and angiogenesis through the regulation of the ERK pathway. The ERK pathway is essential in cell communication.

This study divided diabetic-induced rats with excision wounds into four groups: diabetic control rats, non-diabetic rats, the Drachorhodin perchlorate (DP) treatment group, and the plain base treatment group. Wound healing rates and skin tissue analyses were performed. Diabetic control rats exhibited the slowest healing rates, while diabetic rats treated with DP showed enhanced healing rates. Wound healing in the DP groups was accelerated due to reduced inflammation. By day 14, the DP-treated group had hair follicles and sebaceous glands, a sign of complete and advanced healing. DP also contributed to the reduction of scarring by controlling collagen formation. Collagen formation is essential for healing, but excessive collagen formation can result in scar tissue. The DP group had higher rates of collagen production initially. However, these rates declined by day 21, whereas the control groups still had high collagen production, leading to scar tissue formation. DP also induces the secretion of growth factors and angiogenesis by increasing the production of nitric oxide, which aids in wound healing by delivering blood and vital nutrients to the wound area. This is delayed in diabetic wounds and leads to the condition of chronic wounds that degenerate. Histological analysis revealed that DP did decrease the expression of the TLR4 pathway, leading to a reduction in the expression of cytokines IL-1β and TNF-α.

A meta-analysis by researchers at the University of Traditional Chinese Medicine in China revealed important information about using *Resina draconis* (RC) for diabetic wound healing (Feng et al., 2021). This study identified nine randomized clinical trials using RC for diabetic wound healing. These studies showed that RD can significantly reduce healing time and healing rate in ulcers grades 1 through 3 using the Wagner classification. The studies also demonstrated a 70% reduction in the area of ulcers, shorter hospital stays, and an overall

reduction in the grade of ulcers. Two studies demonstrated a reduction in the frequency and need for dressing changes, and despite some adverse effects, no toxicity contributed to RC.

Angiogenesis and Growth Factors

Curcumin

The formation of new blood vessels, neovasculogenic, is delayed in diabetic wounds, preventing the healing process from progressing (Kant et al., 2015). In order to evaluate the potential of topical curcumin (0.3%) gel derived from *Curcuma longa* in creating new blood vessels in diabetic wounds, this study used diabetic-induced and wounded rats. Tissue samples were evaluated for numerous markers, including but not limited to vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β, and stromal cell-derived growth factor-1alpha (SDF1-α). Rats were divided into three groups: a control with saline-only application, a control group using only the base Pluronic F-127 gel applied topically, and the treatment group of 0.3% curcumin in a base of PF-127 gel. The contents of the PF-127 gel are not described in this study.

Tissue samples were taken throughout the 19-day experiment and preserved for evaluation. Wound closure images were taken to evaluate for wound contraction. Results showed that the curcumin treatment group significantly increased wound closure rates, with the most significant difference occurring on days 3 and 7. Tissue samples revealed that the curcumin treatment group consistently showed increased rates of wound healing with more fibroblast and collagen deposits, fewer inflammatory cells, thicker granulation tissue, more excellent formation of new blood vessels, and complete regeneration of the epithelial layer by day 14. Compared to

the control group, which had significant numbers of inflammatory cells and poured formation of collagen and fibroblast, The study found that curcumin significantly increased the production of TGF-β, VEGF, and SDF1-α, significant factors in wound repair. These factors are found to be significantly delayed or missing in diabetic wounds.

A review study of curcumin derived from turmeric revealed the ability of curcumin to affect nearly all stages of wound healing (Akbik et al., 2006). Curcumin reduces inflammation by inhibiting tumor necrosis factor-alpha (TNF-α) and interleukin-1 (LI-1). Monocytes and macrophages release both of these factors during the inflammation phase of wound healing and can be pronounced in diabetic wounds, thereby extending wound healing time indefinitely. Curcumin also affected the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-(κ)B). This factor is believed to initiate the inflammation phase and is a response to oxidation. Reduction of oxidation plays a role in reducing overall inflammation of a wound, and curcumin is believed to act as an antioxidant in the wound healing process. This was shown in an in vitro study using a lipid peroxidation model in which curcumin's free radical scavenging ability was demonstrated. In other studies, oral curcumin was found to enhance the activity of superoxide dismutase, catalase, and glutathione peroxidase, which are essential enzymes responsible for antioxidant activity in the body. This same activity was also found in topically applied curcumin, which reduced oxidative stress and superoxide radicals.

This same research study found curcumin to significantly affect the proliferation of fibroblast and granulation tissue formation, both vitally important to the proliferation phase of healing. Studies found that myofibroblast migration to the wound site was enhanced and displayed early in wound healing. The early onset of myofibroblast migration to the wound site

allowed for the early formation of granulation tissue and re-epithelialization of the wound, which significantly decreased the time for the wound gap to be closed in clinical trials. The deposit of collagen in wounds is part of the final stage of remodeling and comprises 70-80% of major proteins in the skin. Studies showed greater content of collagen deposits in wounds treated with curcumin, contributing to the higher tensile strength of wounds and evidence of greater migration of fibroblast to the wound area. The final stage of wound healing requires the transforming growth factor β (TGF-β). Curcumin's ability to promote TGF-β was demonstrated by tissue staining, showing an increase in fibroblast and TGF-β over the control—the increase of this growth factor allowed for a greater contraction of wounds by 20% over controls. Additionally, the study found an increase in complete epithelization by 50% over controls, demonstrating curcumin's ability to heal wounds completely.

Herbs with Antibiotic/Antimicrobial Properties

Neem

Neem is known for its antimicrobial and anti-inflammatory effects, ability to induce cell proliferation and immune system modulation (Banerjee et al., 2021). Neem contains known antioxidants, quercetin, amino acids, tannins, and triterpenoids. All of these constituents are identified for their ability to promote wound healing. Topical application of neem seed oil, *Azadirachta indica*, was compared to untreated and positive control of standard diclofenac sodium gel. Rats with excision wounds were created to determine wound healing ability and activities against anti-methicillin-resistant Staphylococcus aureus. MRSA and MSSA strains were isolated from the wounds of clinical patients, and in vivo, treatment with neem oil was

conducted. The timed trials found that after 12 hours of incubation, cell lysis and increased cell permeability were noted, followed by the degeneration of the pathogens. Wound healing models showed a statistically significant difference in swelling, 69%, between the untreated and treated groups. Wound tensile strength was also greatly improved, demonstrating an increase in the collagen matrix compared to the untreated group. However, the positive control group, neomycin cream, displayed a slightly shorter healing period. Wound closure rates displayed similar results, with the positive control group having the shortest closure rates, 10.21 days, followed by the neem treatment group, 11.29 days, and lastly, the untreated group, 13.45 days. This study shows that neem is effective at treating wounds and possesses antibiotic effects comparable to the positive control.

Another study evaluated the effects of neem leaves in vitro against a positive control for the potential of neem to accelerate wound healing (Chundran et al., 2015). Rats were divided into three groups: a negative control group receiving a topical application of 0.9% sodium chloride, the treatment group of neem leaf extract, and a positive control group that received a topical application of povidone-iodine solution. Wound diameter, color, and surface features were used as markers of wound healing. Significant differences were recorded between the negative control group and the neem treatment and positive control groups. The neem and positive control groups displayed similar wound closure rates on days 5 and 15, with the only marked difference being on day 10, where the positive control group slightly increased wound closure over the neem treatment group.

Another in vitro testing was conducted using a bacterial cellulose pulp paste with a Hypericum and Neem oil emulsion applied topically to test efficacy against *Pseudomonas*

aeruginosa and *Staphylococcus aureus* (Villani et al., 2024). Both bacteria commonly infest chronic wounds and can be antibiotic-resistant, and this study aimed to find new strategies for managing infected wounds. The Hypericum oil was derived from the flowering parts; the neem oil was not identified in this study as to whether it was obtained from the leaves or seeds. A 10% solution was used to test against both bacteria. The findings concluded that the paste reduced the number of bacteria and was more effective than the control at reducing *S. aureus* and *P. aeruginosa*. The bacterial cellulose component in this study acted as a moisture and mechanical barrier to aid in wound healing.

St. John's Wort, Hypericum perforatum

A 5% and 10% whole plant extract of *Hypericum perforatum* (HP) was used to create a topical agent in a carboxymethylcellulose base and compared against a control of the same base without the plant extract (Yadollah-Damavandi et al., 2015). Diabetic-induced rats were wounded and divided into the 5% HP group, the 10% HP group, and the control group. The treatment was administered every 24 hours until complete closure of the wound. Skin samples were taken to assess the volume and density of collagen bundles, vessels, and hair follicles. Wound closure rates of the 5% HP group showed the most significant rate of closure, 8.61% per day, followed by the 10% HP group at 6.80% per day. The control group had a significantly lower closure rate at 4.42% per day, demonstrating a clinically significant difference in wound closure rates. Both HP groups had significantly higher populations of fibroblasts, greater density of collagen bundles and hair follicles, and greater length and density of vessels.

In another study, both oral (systemic) and topical applications of *Hypericum perforatum* (HP) were evaluated on diabetic rat models to determine the potential of HP for increasing the

rate of wound healing (Altiparmak et al., 2018). The study utilized several controls and comparison groups on incisional and excisional wounded rats. Group 1 was used as a control and was left untreated; Group 2 was diabetic-induced and left untreated; Group 3 diabetic induced and orally treated; Group 4 diabetic induced with topical treatment; Group 5 diabetic induced with oral olive oil treatment; and Group 6 diabetic induced with topical olive oil treatment. All treatments were carried out for 21 days. Several deaths occurred in the studied rats due to anesthesia, diabetes, and wounding. The most significant number of deaths occurred in the topical olive oil group. Several categories were evaluated for wound healing properties, tensile strength, hydroxyproline concentrations, contraction rates, inflammation, fibroblast activity, collagen density, and epithelialization. Overall, oral HP had the highest effectiveness rates, with topical olive oil being second and topical HP coming third. Both oral and topical HP showed the highest rates of tensile strength, hydroxyproline concentrations, contraction rates, and collagen density. Oral HP had the highest rates in all categories. The concentration of hydroxyproline was critical as few studies examined this factor. Hydroxyproline is a primary amino acid in collagen and thus indicates collagen values. Angiogenesis, another critical factor in wound healing, was more advanced in both HP groups on day 7, but by day 21, all groups displayed relatively the same formation density.

Lavender

Antibiotic resistance is a significant issue with diabetic ulcers, and identifying plant-based antimicrobial and antibacterial sources is of great interest (S Aires et al., 2017). Both lavender *Lavandula angustifolia* and nettle *Urtica diocia* have been identified as potential antimicrobial agents. Nettle extracts contain significant levels of flavonoids, sterols, and

carotenoids and have been shown to have clinical activity against microorganisms. This study emphasized the properties of these plants against MRSA and methicillin-sensitive S. aureus (MSSA), often found in drug-resistant diabetic foot ulcers. Samples of both strains from diabetic foot ulcers were taken as isolates in this study. Ethanol extracts of both plants, lavender, and nettle, were obtained and tested for the total phenolic and flavonoid content. The nettle leaf extract was high in phenolic, caffeic, protocatechuic, and p-coumaric acids. Lavender extracts were also high in phenolics, with hydroxycinnamic, caffeic, and rosmarinic acids being identified. The flavonoids rutin, isoquercetin, and quercetin were identified in nettle, while lavender lacked flavonoids. MRSA and MSSA strains were tested for antibiotic sensitivity to be used as controls in the study. The antibacterial activity of the plant extracts was measured by disc diffusion assay, and the antibacterial activity index was used to compare the plant extracts and positive controls. The final results showed that both lavender and nettle were effective against MSSA and MRSA, with no significant difference identified between the two extracts.

Other studies of lavender evaluated wound healing potential and primary importance and focused on the modulation of macrophage imbalances that cause chronic inflammation and the prevention of healing (Xiang et al., 2023). Macrophages are necessary in the beginning stages of wound healing as they remove debris, destroy germs, and release growth factors. However, simultaneously, they release cytotoxic mediators and are proinflammatory. The Interleukin (IL)-1β expression is a primary pathway induced by macrophages and has been identified as a primary issue in chronic wound healing. This study evaluated the role lavender essential oil (LEO) can play in preventing the release of IL-1β. Mice were used as test subjects, and LPS-induced chronic wounds were created by injecting the wounds with E. coli. The control group

was treated with the exact liposome vehicle as the lavender essential oil group, and skin samples were taken throughout the 12 days of the study. Tumor necrosis factor (TNF-α), IL-6, and IL-1β levels were increased in the LPS-induced mice and contributed to the inflammatory reactions. Lavender essential oil was found to reduce IL-1β inflammatory markers but not TNF-α. This is of primary importance for diabetic wounds as both inflammation markers are increased in diabetic ulcers (Monaghan et al., 2023). This study also found that LEO blocks the release of inflammatory cytokines and inhibits macrophage pyroptosis (inflammatory cell death). This demonstrates that LEO can stop the prolonged inflammatory phase and reduce wound healing time in LPS-induced chronic wounds.

For wound healing, collagen replacement must progress from type III to type I, and granulation tissue must be produced (Mori et al., 2023). Specific growth factors are vital in this process, notably transforming growth factor (TGF-β), PDGF-A, and EGF. This study used a 1% of solution of Lavandula angustifolia solution in a base of 0.1% DMSO and Tween 20 applied to surgically induced wounds on rats. Two groups served as controls: a group that received no treatment after wounding and a control group in which only the base of the treatment group, 0.1% DMSO and Tween 20, was applied. Treatments were applied on alternate days for 14 days, during which the wounds were photographed on the days following treatment—immunohistochemical analysis screened for both collagen type I and III and TGF-β. There was no statistical difference in wound closure rates between the untreated and control groups. In the lavender treatment group, wound closer rates were significantly faster in the first ten days of treatment. The expression of collagen type I and III was more pronounced in the lavender, concluding that increased granulation tissue formation occurred at an early phase in wound

healing than in the untreated and control groups; this allows for a more rapid tissue remodeling process. Additionally, protein levels of TGF-β were significantly increased in the lavender treatment group, and the number of myofibroblasts was increased, demonstrating an increase in the progression of wound healing through the subsequent phases.

A final study aimed to evaluate the species of lavender *Lavandula aspic* syn. *Lavandula latifolia* is used for the essential oil's healing properties and mechanisms (Ben Djemaa et al., 2016). Using excision-wounded female Wistar rats, the study compared the healing potential of *L. aspic* 4% extract against a black vehicle, primarily petrolatum, and a reference drug that contained several plant extracts and other ingredients. Several biochemical components were measured, including lipid peroxidation through malondialdehyde content, glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase enzymes (SOD), with the primary purpose of identifying antioxidant activity. Overall antioxidant levels of the lavender essential oil (LEO) were compared to the antioxidant activity of ascorbic acid. It was found that the antioxidant levels of the LEO were lower than that of ascorbic acid. The LEO-treated rats still displayed high levels of antioxidant activity with increases over the control group of 18.89% for CAT, 83.3% for GPx, and 39.09% for SOD. By the 14th day, the LEO group showed almost identical wounds closer to the reference drug group, demonstrating a comparable ability of LEO in wound healing. Furthermore, autopsies of skin tissue from the LEO and drug treatment groups showed normal epidermal layers in uninjured skin tissue. This comparison shows that LEO is as effective as the reference drug in wound healing, antioxidant activity, and re-epithelization.

Myrrh

Myrrh *Commiphora molmol* contains high levels of sesquiterpenes known to have antiseptic, antibacterial, antifungal, and anti-inflammatory properties (Walsh et al., 2010). Studies have shown myrrh to treat ulcers successfully and as a wound cleanser. Myrrh also possesses antioxidant properties and is a natural analgesic. This current study evaluated the wound-healing potential of myrrh on induced wounds in rabbits (Kamil et al., 2019). The rabbits were divided into two groups: a control group that received irrigation with distilled water only and a treatment group with 10µL of myrrh oil. The study did not specify the number of applications or duration. Wound contraction rates, analysis for inflammatory cells, epithelial thickness, collagen fiber density, and blood vessel analysis were performed on days 3, 7, and 14. Wound contractions showed a significant difference in the treatment group over controls, with the most marked difference being on day 14. The number of inflammatory cells showed a significant difference in the treatment group over the control group, with the most significant difference being on day 3. Epithelial thickness analysis showed a significant difference on each evaluation day, and collagen fiber density showed similar results. Day 3 of the experiment showed the most significant difference in blood vessel count for the treatment group, but by days 7 and 14, there was no significant difference.

Myrrh and honey have a long history of use in medicine, and records show from 1500 BC in the Ebers Papyrus that numerous medicines were made from the combination of myrrh and honey (Walsh et al., 2010). Honey is the only FDA-approved natural remedy for diabetic foot ulcers, and studies show its effectiveness in treating severely infected foot ulcers (Scepankova et al., 2021). In this current study, researchers tested a topical preparation consisting of honey, bee propolis, and myrrh for its ability to heal an infected wound in a 65-year-old male patient with

diabetes mellitus (Lofty et al., 2006). Significant interventions were administered prior to the application of the topical mixture. These included but were not limited to multiple antibiotics, wound debridement, vitamin C and calcium carbonate, vitamins A and E plus zinc, and oral bee propolis. The topical past consisted of 800mg bee propolis and 50 g myrrh mixed with honey in an unspecified amount. Wound cleaning was performed daily, and the paste was applied to fill the cavity. The wound effectively prevented infection, as noted by the lack of pus and cellular exudate. The wound healed completely after four weeks of daily treatment with the paste. Prior to the treatment of the paste, the wound saw no improvement. Several other findings are noted in this study, notably myrrh's ability to reduce cholesterol and triglycerides and to have an antidiabetic effect. Also mentioned are myrrh's antibacterial and antifungal properties against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candia albicans*.

Systematic Review

One systematic review of Traditional Complementary and Alternative Medicine (TCAM) found eighteen medicinal plants effective in treating diabetic foot ulcers (Kumar et al., 2023). These studies were not included in the primary research as they included only one clinical trial for the medicinal plant. Their inclusion in the review is important because they showed substantial importance in healing diabetic wounds and are given a brief review here. Six of these plants included in this review were studied in vitro: Indian mallow *Abutilon indiucm*, snakeroot *Aristolochia indica*, chaparro *Davilla nitida*, lavender *Lavandula angustifolia*, nux-vomica *Strychnos nux-vomica*, and nettle *Utica diocia*. Indian mallow was used as an ethanolic extract of the fruit and demonstrated significant activity against gram-positive and negative bacteria isolated from infected diabetic foot ulcers. Snakeroot was used as a zinc oxide nanoparticle

aqueous extract and was shown to aid in bacterial cell death. Chaparro bark was extracted in ethanol and demonstrated significant antimicrobial activity and inhibition of multidrug-resistant bacteria in diabetic ulcers. Chaparro was also demonstrated to be an excellent adjunctive agent with traditional antibiotic treatment (Perim et al., 2019). Nux-vomica is used as a zinc oxide nanoparticle aqueous extract and has been demonstrated to be used against multidrug-resistant bacteria (Kumar et al., 2023).

This systemic review found four effective plants in in vivo models: aloe *vera*, onosma *microcarpum*, Chinese foxglove *Rehmannia glutinosa*, and felty germander *Teucrium polium*. Onosma root was extracted using hexane and was shown to accelerate diabetic wound healing, with complete healing after 20 days. Chinese foxglove was used as a whole plant water extract, reducing the overall ulcer area by increasing the vascular endothelial growth factor. The felty germander study used the whole fruit in an ethanol extract as a 10% ointment with increased healing rates of diabetic ulcers over controls.

Further, two case reports and eight clinical trials were included comprising seven herbs not already mentioned: kiwifruit *Actinidia deliciosa, Ageratina pichinchensis*, neem *Axadirachta indica*, coffee *Coffea canephora*, yellow sweet clover *Melilotus officinalis*, myrtle *Myrtus communis*, Mecca galls *Quercus infectoria* and gurjo *Tinospora cordifolia*. Pure kiwifruit extract significantly reduced the size of foot ulcers over the control by increasing collagen and granulation tissue production. Coffee fruit extract increased wound healing by forming granulation tissue and reduced infections during a 4-day treatment period. Yellow sweet clover reduced the total area of the foot ulcer, and Mecca galls reduced wound size with long-term

treatment. Finally, gurjo reduced the need for debridement. These herbs represent potential therapies for diabetic ulcers and warrant further investigation.

Discussion

Numerous herbs have been studied in clinical trials for their potential in topically treating diabetic ulcers. These herbs were able to target several of the primary processes in wound healing that are dysregulated in DUs, causing delayed healing. The four stages of wound healing must occur properly and within healthy time ranges, or increased inflammation will occur (Monaghan et al., 2023). These stages are hemostasis, inflammation, proliferation, and remodeling. The most studied area of wound closure rates is part of the remodeling stage but is inhibited by earlier stages, particularly inflammation. In most studies that evaluated wound closure rates, saline solution was used to wash the wounds before applying the studied treatments, and then sterile dressings were used to cover the wounds. Some studies administered antibiotics to participants in conjunction with the studied treatment. This stresses a critical issue of focusing on wound closure rates, taking a full-picture approach, and including multiple herbs that target all of the essential cofactors of DUs into consideration.

Herbs included in this review that were evaluated only for wound closure rates all showed a significant ability to increase the closure rate. Plantago or plantain, calendula, rosemary, eucalyptus, and olive oil were the herbs evaluated solely for wound closure. Olive oil holds particular importance as it is the only studied plant that can be used as a carrier base for other herbs. Olive oil's ability to aid in wound healing by itself is remarkable, and in conjunction

with other herbs, the potential use is extraordinary (Abdoli et al., 2022). Of the remaining herbs mentioned above, plantain and calendula are widely known for their wound healing and topical applications among herbalists. With both of these plants, clinical trials were conducted with human participants, which gives excellent supportive evidence for their use in a topical formula. However, neither plant directly addressed the issue of infections, and in the plantain study, antibiotics were administered to participants (Ghanadian et al., 2022). In the calendula study on diabetic ulcers, it was not specified whether other adjunct treatments, such as antibiotics, were used (Buzz et al., 2016). The study mentions that other healing medications or supportive therapies were not used, but oral antibiotics were not listed. The study also mentions that calendula was effective against the tested pathogens but does not list the pathogens. Also mentioned was the reduction in unpleasant odor and the decrease in colonization, which mentions a reference table that was not available. This information suggests that calendula is effective at preventing infection. However, specific studies would need to be conducted to confirm calendula's ability to combat gram-positive and gram-negative bacteria found in DUs.

Rosemary and eucalyptus utilized rat and in vitro studies to determine their potential for healing DUs. Both models allow for further analysis of tissue samples and untreated controls, which is unethical in human trials. Rosemary was effective at increasing the formation of granulation tissue and re-epithelization (Abu-Al-Basal, M., 2010). The control group in the study had significantly delayed healing and increased inflammation with high levels of neutrophils, signaling that rosemary helps promote wound healing by reducing inflammation and allowing for later stages of wound healing to progress. Rosemary had one human trial in patients with pressure ulcers, providing evidence that rosemary was effective at increasing wound closure

rates (Parizi et al., 2022). Rosemary has also effectively treated C. albicans (Nejati et al., 2015). C. albicans is present on the skin, frequently colonizes open wounds, and can cause severe complications. Eucalyptus was included in a study along with rosemary and lavender and was shown to increase the effectiveness of rosemary in combating C. albicans (El-Sakhawy et al., 2023). This study demonstrates an essential synergistic effect between the herbs and combined herbs, all indicated for use in diabetic ulcers.

Both eucalyptus and lavender possess significant potential in healing DUs. In vitro studies of eucalyptus extract demonstrate its potential to have antidiabetic effects in conjunction with being antioxidant and antimicrobial (Mumtaz et al., 2022). Reducing the microbial and bacterial load reduces inflammation as cells cease to signal to the immune system that there is a foreign invader. Lavender, combined with nettle, was effective against MRSA and MSSA found in drug-resistant DUs (S Aires et al., 2017). Lavender was also effective at modulating macrophages, which play a role in proinflammation signals (Xiang et al., 2023). Lavender emerged throughout this study as an herb of primary importance. It also modulates TNF-α, IL-6, and IL-1β and promotes collagen production to progress from type III to type I while increasing TNF-β (Mori et al., 2023). The latter is a vital change from the inflammatory promoting TNF-α, which can inhibit progression through the healing stages. The antioxidant ability of lavender has also been studied, and lavender was found to have high levels of antioxidant activity for GPx, CAT, and SOD (Ben Djemaa et al., 2016). Dragon's blood had similar effects, effectively modulating TNF-α and COX-2, reducing the inflammation response, and allowing for collagen formation and wound healing (Xiong et al., 2022). Dragon's blood also aided in angiogenesis and

nitric oxide production, increasing blood flow to wound sites. Aloe vera has increased angiogenesis and nitric oxide production (Panahi et al., 2015; Massoud et al., 2022).

Aloe has effects on another important pathway, matrix metalloproteinase (MMP)-9 enzymes, which are vital for the degradation of the ECM (Junren Chen et al., 2022). MMP-9 must be carefully regulated, or excessive degradation will occur. Aloe was found to be an excellent modulator of this enzyme and to improve granulation tissue formation. The healing effects of aloe in combination with olive oil were found to be enhanced, which supports the prior theory of using olive oil as a carrier for these herbs (Panahi et al., 2015). Curcumin derived from turmeric also promotes angiogenesis and growth factors necessary for wound healing (Kant et al., 2015). Curcumin was the only herb shown to increase growth factors significantly and is a vital extract for any diabetic wound preparation. Curcumin increases growth factors and the production of collagen and fibroblasts, completely regenerating the epithelial layer. Curcumin combines the effects of nearly all the herbs mentioned above into one potent extract. Curcumin combined with an antimicrobial and antibiotic agent such as lavender can affect nearly every stage of wound healing.

Two other antibiotic herbs stand out as having high potential for use in combination with either curcumin or other herbs: neem and St. John's Wort. Neem is well known for its antimicrobial and anti-inflammatory effects and contains well-known antioxidants (Banerjee et al., 2021). Like lavender, neem has biological effects on MRSA and MSSA strains isolated from diabetic patients. Neem oil also showed action against Pseudomonas aeruginosa and was more effective than the control (Villani et al., 2024). Neem also reduced swelling, increased wound tensile strength, and positively affected wound closure rates (Banerjee et al., 2021). St. John's is

the last herb included in this study. It was primarily evaluated for wound closure and collagen production but was found to advance angiogenesis and increase tensile strength and wound contraction rates (Altiparmak et al., 2018).

Conclusion

The herbs discussed have been shown to affect every aspect of wound healing in diabetic ulcers. While it is possible to include every herb in a single preparation, choosing the herbs that cover the primary areas of concern: wound closure, bacterial and microbial infection, inflammation, and control of growth factors, and having a synergistic effect with each other will be significant in their effects. Clinical trials should begin by focusing on combining three or four herbs to provide healing and comfort to the patient and assess their effects. The delivery method is of great importance, and a future literature review could be conducted to evaluate the best carriers and bases for topical preparation along with agents that allow for greater delivery and proper wound care. Herbal preparations could be used for wound cleansing as well and used in place of pure saline solution to aid in wound healing. Studies not covered in this paper on herbal preparations for wound washing are available. This paper focused solely on topical preparations, but addressing the internal body processes and control of blood sugar is essential to prevent the occurrence of diabetic ulcers. This is another area where herbal medicine can provide significant benefits.

References

Abdoli, A., Shahbazi, R., Zoghi, G., Davoodian, P., Kheirandish, S., Azad, M., & Kheirandish, M. (2022). The effect of topical olive oil dressing on the healing of grade 1 and 2 diabetic foot ulcers: An assessor-blind randomized controlled trial in type 2 diabetes patients. Diabetes & metabolic syndrome, 16(12), 102678. https://doi.org/10.1016/j.dsx.2022.102678

Abu-Al-Basal, M. A. (2010). Healing potential of Rosmarinus officinalis L. on full-thickness excision cutaneous wounds in alloxan-induced-diabetic BALB/c mice. Journal of Ethnopharmacology, 131(2), 443–450. https://doi.org/10.1016/j.jep.2010.07.007

Akbik, D., Ghadiri, M., Chrzanowski, W., & Rohanizadeh, R. (2014). Curcumin as a wound healing agent. Life Sciences, 116(1), 1–7. https://doi.org/10.1016/j.lfs.2014.08.016

Altıparmak, M. & Eskitaşçıoğlu, T. (2018). Comparison of Systemic and Topical Hypericum Perforatum on Diabetic Surgical Wounds. Journal of Investigative Surgery, 31(1), 29–37. https://doi.org/10.1080/08941939.2016.1272654

Aqsa T., Shafique M.S., Qureshi U. (n.d.). Efficacy of aloe vera cream for healing diabetic foot ulcers. J Rawalpindi Med Coll. 2019;23:113–125.

Banerjee, K., Chatterjee, M., Sandur V, R., Nachimuthu, R., Madhyastha, H., & Thiagarajan, P. (2021). Azadirachta indica A. Juss (Neem) oil topical formulation with liquid crystals ensconcing depot water for anti-inflammatory, wound healing, and anti-methicillin resistant Staphylococcus aureus activities. Journal of Drug Delivery Science and Technology, p. 64. https://doi.org/10.1016/j.jddst.2021.102563

Ben Djemaa, F. G., Bellassoued, K., Zouari, S., El Feki, A., & Ammar, E. (2016). Antioxidant and wound healing activity of Lavandula aspic L. ointment. Journal of Tissue Viability, 25(4), 193–200. https://doi.org/10.1016/j.jtv.2016.10.002

Boukeloua, A., Kouadria, M., Bendif, H., Plavan, G., Alsalamah, S. A., Alghonaim, M. I., Boufahja, F., & Abd-Elkader, O. H. (2023). Physicochemical Analysis and Wound Healing Activity of Azadirachta indica (A. Juss) Fruits. Processes, 11(6), 1692. https://doi.org/10.3390/pr11061692

Buzzi, M., de Freitas, F., & Winter, M. (2016). A Prospective, Descriptive Study to Assess the Clinical Benefits of Using Calendula officinalis Hydroglycolic Extract for the Topical Treatment of Diabetic Foot Ulcers. Ostomy/wound management, 62(3), 8–24.

Chundran, N., Husen, R., & Rubianti, R. (2015). Effect of Neem Leaves Extract (Azadirachta Indica) on Wound Healing. Althea Medical Journal, 2(2), 199–207. https://doi.org/10.15850/amj.v2n2.535

El-Sakhawy, M., Soliman, G., El-Sheikh, H., & Ganaie, M. (2023). Anticandidal effect of Eucalyptus oil and three isolated compounds on cutaneous wound healing in rats. European Review for Medical and Pharmacological Sciences, 27.

Faraji, N., Parizad, N., Goli, R., Nikkhah, F., & Golhkar, M. (2023). Fighting diabetic foot ulcer by combination therapy, including larva therapy, Medi honey ointment, and silver alginate dressings: A case report. International Journal of Surgery Case Reports, 113, N.PAG. https://doi.org/10.1016/j.ijscr.2023.109055

Feng, H., Huang, W., Zhou, Q., Liu, T., Li, H., & Yue, R. (2023). Efficacy and safety of Resina Draconis for wound repair in the treatment of diabetic foot ulcer: A systematic review

and meta-analysis of randomized controlled trials. Complementary Therapies in Clinical Practice, p. 50, N.PAG. https://doi.org/10.1016/j.ctcp.2022.101707

Ghanadian, M., Soltani, R., Homayouni, A., Khorvash, F., Jouabadi, S. M., & Abdollahzadeh, M. (2022). The Effect of Plantago major Hydroalcoholic Extract on the Healing of Diabetic Foot and Pressure Ulcers: A Randomized Open-Label Controlled Clinical Trial. The international journal of lower extremity wounds, 15347346211070723. Advance online publication. https://doi.org/10.1177/15347346211070723

Giostri, G. S., Novak, E. M., Buzzi, M., & Guarita-Souza, L. C. (2022). Treatment of acute wounds in hand with Calendula officinalis L.: A randomized trial. Tissue barriers, 10(3), 1994822. https://doi.org/10.1080/21688370.2021.1994822

Jayalakshmi, M. S. (2020). Effect of neem leaves extract irrigation on the wound healing outcome in nurse managed diabetic foot ulcers. National Journal of Physiology, Pharmacy & Pharmacology, 10(10), 915–921. https://doi.org/10.5455/njppp.2021.10.09238202008092020

Junren Chen, Siqi Qin, Shengmeng Liu, Kexin Zhong, Yiqi Jing, Xuan Wu, Fu Peng, Dan Li, & Cheng Peng. (2023). Targeting matrix metalloproteases in diabetic wound healing. Frontiers in Immunology, 1–19. https://doi.org/10.3389/fimmu.2023.1089001

Kamil, N. & Al-Ghaban, N. (2019). Evaluation of effect of local exogenous application of Myrrh oil on healing of wound incisions of facial skin (Histochemical, Histological and Histomorphometrical study in rabbits). Journal of Baghdad College of Dentistry, 31(4). https://doi.org/10.26477/jbcd.v31i4.2724

Kant, V., Gopal, A., Kumar, D., Pathak, N. N., Ram, M., Jangir, B. L., Tandan, S. K., & Kumar, D. (2015). Curcumin-induced angiogenesis hastens wound healing in diabetic rats. The Journal of Surgical Research, 193(2), 978–988. https://doi.org/10.1016/j.jss.2014.10.019

Kumar, S., Bharali, A., Sarma, H., Kushari, S., Gam, S., Hazarika, I., Prasad, S. K., & Laloo, D. (2023). Traditional complementary and alternative medicine (TCAM) for diabetic foot ulcer management: A systematic review. Journal of Ayurveda and Integrative Medicine, 14(4). https://doi.org/10.1016/j.jaim.2023.100745

Lotfy, M., Badra, G., Burham, W., & Alenzi, F. Q. (2006). Combined use of honey, bee propolis and myrrh in healing a deep, infected wound in a patient with diabetes mellitus. British Journal of Biomedical Science, 63(4), 171–173. https://doi.org/10.1080/09674845.2006.11732742

Ma, X.-X., Liu, Q.-K., Kuai, L., Ma, X., Luo, Y., Luo, Y., Song, J.-K., Fei, X.-Y., Jiang, J.-S., Wang, M.-X., Shen, F., Ru, Y., & Li, B. (2023). The role of neutrophils in diabetic ulcers and targeting therapeutic strategies. International Immunopharmacology, 124(Pt A), 110861. https://doi.org/10.1016/j.intimp.2023.110861

Massoud, D., Fouda, M. M. A., Sarhan, M., Salama, S. G., & Khalifa, H. S. (2022). Topical application of aloe gel and olive oil combination promotes the wound-healing properties of streptozotocin-induced diabetic rats. Environmental Science and Pollution Research International, 29(39), 59727–59735. https://doi.org/10.1007/s11356-022-20100-9

Mehmet Altıparmak, & Teoman Eskitaşçıoğlu. (2018). Comparison of Systemic and Topical Hypericum Perforatum on Diabetic Surgical Wounds. Journal of Investigative Surgery, 31(1), 29–37. https://doi.org/10.1080/08941939.2016.1272654

Monaghan, M. G., Borah, R., Thomsen, C., & Browne, S. (2023). Thou shall not heal: Overcoming the non-healing behaviour of diabetic foot ulcers by engineering the inflammatory microenvironment. Advanced Drug Delivery Reviews, p. 203. https://doi.org/10.1016/j.addr.2023.115120

Mori, HM, Kawanami, H., Kawahata, H, Aoki, M. (2016). Wound healing potential of lavender oil by acceleration of granulation and wound contraction through induction of TGF-β in a rat model. BMC Complement Altern Med. 2016 May 26;16:144. doi: 10.1186/s12906-016-1128-7. PMID: 27229681; PMCID: PMC4880962.

Mumtaz, R., Zubair, M., Khan, M. A., Muzammil, S., & Siddique, M. H. (2022). Extracts of Eucalyptus alba Promote Diabetic Wound Healing by Inhibiting α-Glucosidase and Stimulating Cell Proliferation. Evidence-Based Complementary & Alternative Medicine (ECAM), 1–12. https://doi.org/10.1155/2022/4953105

Naveen Kumar Chundran, Ike Rostikawati Husen, & Irra Rubianti. (2015). Effect of Neem Leaves Extract (Azadirachta Indica) on Wound Healing. Althea Medical Journal, 2(2), 199–207. https://doi.org/10.15850/amj.v2n2.535

Nawar Bahjet Kamil, & Nada M. Al-Ghaban. (2019). Evaluation of effect of local exogenous application of Myrrh oil on healing of wound incisions of facial skin (Histochemical, Histological and Histomorphometrical study in rabbits). Journal of Baghdad College of Dentistry, 31(4).

Nejati, H., Farahpour, M., & Nagadehi, M. (2015). Topical rosemary officinalis essential oil improves wound healing against disseminated Candida albicans infection in rat model.

Comparative Clinical Pathology, 24(6), 1377–1383. https://doi.org/10.1007/s00580-015-2086-z

Panahi, Y., Izadi, M., Sayyadi, N., Rezaee, R., Jonaidi-Jafari, N., Beiraghdar, F., Zamani, A., & Sahebkar, A. (2015). Comparative trial of Aloe vera/olive oil combination cream versus phenytoin cream in treating chronic wounds. Journal of wound care, 24(10), 459–465. https://doi.org/10.12968/jowc.2015.24.10.459

Parizi, F., Sadeghi, T., & Heidari, S. (2021). The effect of rosemary ointment on the grade I pressure ulcers in ICU patients: A randomized clinical trial. Nursing Practice Today, 9(1). https://doi.org/10.18502/npt.v9i1.7321

Perim, M., Borges, J., Lima da Silva, E., Araújo, T., Oliveira da Silva, A., Christiane da Silva, V., Carreiro, S., Cunha, A., Pranchevicius, M. 2019. In vitro antibacterial and time-kill assay of ethanolic extract of Davilla nitida bark on multidrug resistant bacteria isolated from diabetic foot lesions. Nat Prod Res. 2019 Aug;33(16):2383-2388. doi: 10.1080/14786419.2018.1443085. Epub 2018 Feb 23. PMID: 29475383.

S Aires A., Dias C., Saavedra M.J., Fernandes C. (2017). Antibacterial potential of Urtica dioica and Lavandula angustifolia extracts against methicillin-resistant Staphylococcus aureus isolated from diabetic foot ulcers. J Herb Med. 2017;10:53–58. doi: 10.1016/j.hermed.2017.05.003.

S. Villani, S. Kunjalukkal Padmanabhan, M. Stoppa, R. Nisi, M. Calcagnile, P. Alifano, C. Demitri, & A. Licciulli. (2024). Neem-hypericum-bacterial cellulose wound care paste characterized in vitro and in Galleria mellonella in vivo model. Carbohydrate Polymer Technologies and Applications, 7(100431-). https://doi.org/10.1016/j.carpta.2024.100431

Silva, A. C. C., Eugênio, A. N., Mariano, S. S., Poletti, S., Gaspi, F. G., Bittencourt, J. V. S., Casagrande, L. R., Silveira, P. C. L., Esquisatto, M. A. M., Aro, A. A., Andrade, T. A. M., & Santos, G. M. T. (2021). Topical application of Azadirachta indica improves epidermal wound healing in hyperglycemic rats. Comparative Clinical Pathology, 30(3), 461–472. https://doi.org/10.1007/s00580-021-03240-1

Somayeh Yahya, & Zahra Mehraban. (2020). Effect of Hypericum perforatum cream on perineal wound healing in primiparous women. Majallah-i Zanān, Māmā̓ī va Nāzā̓ī-i Īrān, 23(6), 61–69. https://doi.org/10.22038/ijogi.2020.16881

Süntar, I. P., Akkol, E. K., Yilmazer, D., Baykal, T., Kirmizibekmez, H., Alper, M., & Yeşilada, E. (2010). Investigations on the in vivo wound healing potential of Hypericum perforatum L. Journal of Ethnopharmacology, 127(2), 468–477. https://doi.org/10.1016/j.jep.2009.10.011

Tamam El-Elimat, Haya S. El-Qaderi, Wael M. Hananeh, Mahmoud M. Abu AlSamen, Ahmed H. Al Sharie, Musa A. Alshehabat, Mohammad Al-Gharaibeh, & Feras Q. Alali. (2023). Evaluation of the Wound Healing Potential of Hypericum triquetrifolium Turra: An Experimental Animal Study and Histopathological Examination. Scientia Pharmaceutica, 91(1), 16. https://doi.org/10.3390/scipharm91010016

Ulbricht, C. (2010). Natural standard herb and supplement guide. Elsevier

Villani, S., Kunjalukkal Padmanabhan, S., Stoppa, M., Nisi, R., Calcagnile, M., Alifano, P., Demitri, C., & Licciulli, A.. (2024). Neem-hypericum-bacterial cellulose wound care paste characterized in vitro and in Galleria mellonella in vivo model. Carbohydrate

Polymer Technologies and Applications, 7(100431-). https://doi.org/10.1016/j.carpta.2024.100431

Walsh, M. E., Reis, D., & Jones, T. (2010). Integrating complementary and alternative medicine: use of myrrh in wound management. Journal of Vascular Nursing : Official Publication of the Society for Peripheral Vascular Nursing, 28(3), 102. https://doi.org/10.1016/j.jvn.2010.06.001

Xiang Ao, Huan Yan, Mei Huang, Wei Xing, Luo-Quan Ao, Xiao-Feng Wu, Cheng-Xiu Pu, Bao-Yue Zhang, Xiang Xu, Hua-Ping Liang, & Wei Guo. (2023). Lavender essential oil accelerates lipopolysaccharide-induced chronic wound healing by inhibiting caspase-11-mediated macrophage pyroptosis. Kaohsiung Journal of Medical Sciences, 39(5), 511–521. https://doi.org/10.1002/kjm2.12654

Xiong, Z., Huo, M., Jia, Y., Zhou, C., Ma, X., Yin, H., Jiang, X., & Yu, W. (2022). Dracorhodin Perchlorate Regulates the Expression of Inflammatory Cytokines through the TLR4 Pathway and Improves Skin Wound Healing in Diabetic Rats. Evidence-Based Complementary & Alternative Medicine (ECAM), pp 1–12. https://doi.org/10.1155/2022/9050686

Yadollah-Damavandi, S., Chavoshi-Nejad, M., Jangholi, E., Nekouyian, N., Hosseini, S., Seifaee, A., Rafiee, S., Karimi, H., Ashkani-Esfahani, S., Parsa, Y., & Mohsenikia, M. (2015). Topical Hypericum perforatum Improves Tissue Regeneration in Full-Thickness Excisional Wounds in Diabetic Rat Model. Evidence-Based Complementary & Alternative Medicine (ECAM), 2015, 1–4. https://doi.org/10.1155/2015/245328

Yunita Sari MHS, P., Iwan Purnawan MKep, Dhadhang Wahyu Kurniawan MSc, A., & Eman Sutrisna Dr, Mk. (2018). A Comparative Study of the Effects of Oil Gel and Aloe Vera Gel on Wound Healing in Diabetic Rats. Journal of Evidence-Based Integrative Medicine, 23. https://doi.org/10.1177/2515690X18772804