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Diabetic wound healing with medicinal plants: Past and present approaches

Diyabetik yaraların bitkisel tedavisi: Geçmişten günümüze yaklaşımlar

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ABSTRACT

Diabetic wounds are characterized by their tendency to heal slowly, exhibit persistent inflammation, and become readily infected, which significantly complicates the overall wound-healing process. While conventional treatments often fall short in delivering lasting solutions, medicinal plants have emerged as a promising alternative for wound care. Rooted in ancient healing traditions, these herbal remedies are now gaining scientific recognition for their effectiveness in managing diabetic wounds. Compounds such as flavonoids, alkaloids, tannins, and terpenoids contribute to wound healing by exhibiting antimicrobial, anti-inflammatory, antioxidant, and angiogenic properties. These bioactive constituents accelerate tissue regeneration while minimizing complications, making them valuable in diabetic wound management. This review aims to connect traditional herbal wisdom with modern scientific insights by exploring key medicinal plants, their phytochemical mechanisms, and their therapeutic benefits in wound healing. With further clinical research and advancements in biotechnology, these natural remedies could become integral to mainstream diabetic wound care, providing safer, more affordable, and sustainable treatment options.

Keywords: Diabetic wounds, herbal medicine, phytotherapy, tissue regeneration, angiogenesis, inflammation

ÖZET

Diyabetik yaralar, yavaş iyileşme, sürekli iltihaplanma ve kolayca enfekte olmaları ile karakterizedir; bu durum, yara iyileşme sürecini önemli ölçüde zorlaştırır. Konvansiyonel tedaviler çoğu zaman kalıcı çözümler sunmakta yetersiz kalırken, tıbbi bitkiler yara bakımında umut verici bir alternatif olarak öne çıkmaktadır. Kadim şifa geleneklerine dayanan bu bitkisel çözümler, günümüzde diyabetik yaraların yönetiminde etkinlikleri açısından bilimsel olarak da tanınmaktadır. Flavonoidler, alkaloidler, tanenler ve terpenoidler gibi bileşikler; antimikrobiyal, anti-inflamatuar, antioksidan ve anjiyojenik özellikleri sayesinde yara iyileşmesini desteklemektedir. Bu biyoaktif bileşenler, komplikasyonları minimize ederken doku rejenerasyonunu hızlandırmakta ve diyabetik yara yönetiminde değerli bir rol oynamaktadır. Bu derleme, geleneksel bitki bilgeliğini modern bilimsel bulgularla birleştirmeyi amaçlayarak, başlıca tıbbi bitkileri, fitokimyasal mekanizmalarını ve yara iyileşmesindeki terapötik faydalarını incelemektedir. Daha fazla klinik araştırma ve biyoteknolojik gelişmeler ile bu doğal çözümler, diyabetik yara bakımında daha güvenli, uygun maliyetli ve sürdürülebilir tedavi seçenekleri sunarak ana akım tedavinin ayrılmaz bir parçası hâline gelebilir.

Anahtar kelimeler: Diyabetik yaralar, bitkisel ilaç, fitoterapi, doku rejenerasyonu, anjiyogenez, inflamasyon

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Diabetes mellitus is a chronic metabolic condition characterised by persistently high blood sugar levels, which can induce a range of issues, including slow-healing wounds. Among these, diabetic foot ulcers pose a major challenge in clinical settings due to prolonged inflammation, poor blood vessel formation, reduced collagen production, and an increased risk of infection (Zhao et al., 2016). While conventional treatments such as antibiotics, wound dressings, and surgical interventions are commonly used, they often fail to achieve optimal healing, prompting the need for alternative therapies.

For centuries, traditional medicine relied heavily on herbal remedies and healing systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani medicine, particularly in wound care and tissue repair. These natural remedies are abundant in bioactive chemicals, including flavonoids, alkaloids, tannins, saponins, and terpenoids which exhibit powerful antioxidant, antimicrobial, anti-inflammatory, and angiogenic properties. Scientific studies have increasingly supported the effectiveness of these phytochemicals in modulating key biological processes involved in wound healing, such as neutralizing reactive oxygen species (ROS), regulating inflammatory cytokines, and promoting extracellular matrix remodeling (Pathak & Mazumder, 2024).

Despite growing recognition of herbal medicine in diabetic wound healing, a significant gap remains in integrating traditional knowledge with modern biomedical research. A systematic investigation into medicinal plants, their active compounds, and their mechanisms of action is critical for establishing their effectiveness, safety, and practical application in clinical settings. This review seeks to bridge the gap between traditional wisdom and scientific validation by providing an in-depth analysis of therapeutic herbs with proven wound-healing potential in diabetes. By understanding how these plant-based compounds support tissue repair, researchers and healthcare professionals can explore innovative, cost-effective, and sustainable treatment approaches for diabetic wound care.

Healing wounds in a diabetic model using medicinal herbs

In Africa and other poor countries, ethnobotanical research has found several plant and herb species that can help heal wounds. Using medicinal herbs to treat and care for wounds involves creating a suitable environment for natural healing, along with cleaning and removing necrotic tissue. The use and administration of medicinal herbs for wound treatment in both diabetic and non-diabetic cases has recently received fresh attention since it is thought that their constituents are less harmful and possess fewer adverse effects than conventional therapeutic treatments (Figure 1). The application of medicinal herbs is one among the therapeutic techniques used in therapy, especially in low-resource settings, since impaired healing of diabetes wounds is considered a serious illness concern aimed at health experts across the globe, and it is connected to an unknown etiology in certain situations (Kumar et al., 2007).

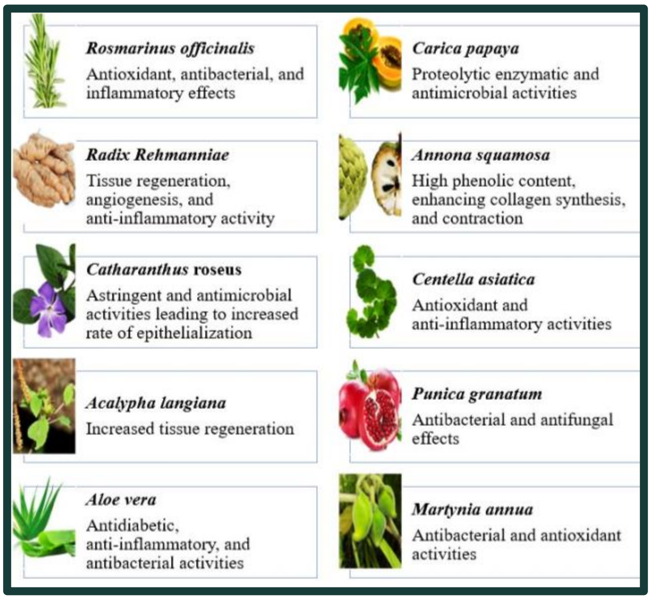

Figure 1. The therapeutic impact of medicinal herbs on diabetic patients (Pang et al., 2019)

Salvia rosmarinus Spenn.

Inflammatory drugs and the antibacterial properties of this plant are well investigated. The study evaluated the ability of the plant extract to heal full-thickness excision wounds in BALB/c mice induced with diabetes using alloxan. Male BALB/c mice weighing 18–20 g and aged 6 weeks were used in this study. In this investigation, 0.2 cc of alloxan monohydrate was intraperitoneally injected to cause diabetes in the mice. Only those animals were employed in the experiment that developed diabetes after receiving an injection of alloxan. Many tests, including those for the following procedures, were carried out: wound contraction, granulation tissue, and histopathology trial. The weight of the granulation tissue on day 3 rose significantly when compared to the untreated controls, according to the results. The initial size of the wound both before and after debridement, as well as the progression of the wound towards closure, were consistently measured quantitatively. The percentage decrease in the size of the wound during days 3, 6, 10, and 15 following the injury was used to calculate the wound contraction rate. In the group treated with the extract as opposed to the untreated, a significant improvement in the proportion of contraction of the wound was seen. The healing process was improved in the treated group on days 6 and 15 following injury, according to a histological analysis. When topically applied to diabetic mouse wounds, the aqueous extract and the plant's aerial parts showed significantly greater healing effects, likely due to their antibacterial, anti-inflammatory, and antioxidant properties (Gurib-Fakim, 2006). In the names and figures of the therapeutic plants are shown in Figures 2-12.

Figure 2. *Salvia rosmarinus* Spenn.

Carica papaya

The antibacterial, anti-inflammatory, and antioxidant properties of unripe *C. papaya* fruit juice have been reported (Budovsky et al., 2015). The research processed the fruits to study how well *C. papaya* heals wounds in a diabetic rat model, following the procedure described above. Morton and Malone's technique was used to give rats excision wounds after they were given diabetes (Suja et al., 2020). Animals were given 1 cc of intravenous ketamine hydrochloride to put them to sleep before having their backs shaved using an electric clipper on both sides. A full-thickness circular excision wound was created along a defined region. Animals were watched for any signs of infection while the incision was left exposed. Animals that displayed infection-related symptoms were replaced and removed from the research. Six animals were placed in each of the five groups (Groups 1–5). An extract of *C. papaya* was applied topically to the diabetic experimental group's animals in Group 4, and wound measurements were taken during days 1-5 and 11 across every group. According to the scientists, rats given fruit extract showed a considerable rise in the activity of their ability to mend wounds. As compared to the animals in groups 1, 3, and 5, those in Groups 2 and 4 demonstrated a shorter epithelialization time and a greater percentage of recovered wound contraction corresponding to the excision-damaged model. Compared to the normal and diabetic control groups, the extract-treated animals in Groups 2 and 4 showed significantly higher levels of hydroxyproline. Both the dry and moist weights granulation tissues inside the mice treated with the extract significantly increased. The animals that did not receive the extract developed wounds that were hard, crusty, and poorly defined. Diabetes is known to cause a variety of distinct and interrelated wound healing deficits, including reduced blood flow increased oxygen release brought on by high blood sugar, lowered collagen or fibronectin synthesis brought on by protein deficiency, weakened local immunological and cell defences, as well as decreased anabolic activity brought on by low insulin and growth hormone levels. Neutrophil migration, chemotaxis, adherence, and other functions are similarly impacted by hyperglycemia. Papain and chymopapain, two of the main components of *C. papaya*, have proteolytic enzyme activity and antibacterial activity, which are associated with the fruit's ability to heal wounds. The absence of biofilm seen in diabetic mice given the extract treatment demonstrates that the enzyme components of *C. papaya* might compromise the biofilm defences that prevent exposure to oxygen and UV radiation and promote bacterial imbalance. Papain in *C. papaya* supports wound healing by promoting enzymatic debridement and tissue remodeling. Additionally, vitamin C-rich foods are crucial for the conversion of proline into hydroxyproline, an important step in collagen formation and tissue repair (Li et al., 2023; Nayak et al., 2007).

Figure 3. *Carica papaya* (Akanda et al., 2025)

Radix Rehmanniae

It has been discussed how traditional Chinese medicine uses *Radix Rehmanniae* to treat foot ulcers. Albino Wistar female rats were used, along with Sprague Dawley female rats, which are often employed in ulcer and diabetes studies, including inflammation models, to examine the wound-healing effects of *Radix Rehmanniae* in an experimental diabetic foot ulcer model in animals. In this research, diabetes and foot ulcers were induced using the traditional method. In a rat model of diabetic foot ulcers, wound healing in the *Radix Rehmanniae*-treated group was assessed and compared with the control group receiving freshwater on days 4, 8, 13, and 18. Among a group that was given *Radix Rehmanniae* extracts, a substantial decrease in the ulceration area was seen between days eight through eighteen. When it comes to tissue regeneration, epithelialisation, and scar development were generally well established, animals receiving *Radix Rehmanniae* extract were compared with a control group administered only water to assess the extract's wound-healing effects. A crucial point to remember is that animals given a considerable amount of *Radix Rehmanniae* extract showed VEGF expression beginning on day 4 and continuing until day 13. Angiogenesis has reportedly been inhibited by diabetes (Lau et al., 2012). Via the mechanisms of regrowth of blood vessels, inflammation, and tissue management, *Radix Rehmanniae* revealed its efficiency in aiding rats with diabetic foot ulcers recover.

Figure 4. *Radix Rehmanniae*

Annona squamosa

Custard apple is another name for *Annona squamosa*. *A. squamosa* (sugar apple) is not native to India. It originated in tropical America and is now grown in India and many tropical regions worldwide. Locals use the leaves and seeds to treat diabetes and other ailments, including fever and ulcers (Ponrasu & Suguna, 2014). The effectiveness of the plant's ethanolic leaf extract in rats with streptozotocin (STZ)-induced diabetes and its effects on wound healing were evaluated by Ponrasu and Suguna (Ponrasu & Suguna, 2012). For the experiment, male Wistar rats in better health were given STZ (50 mg/kg of body weight) through the abdomen once to cause diabetes. Rats were shaved from the rear after being rendered diabetic, likewise, a 2 cm2 complete open excision incision was created by removing a piece of skin under anaesthesia. Rats in the treated group received 200 µL of extract (100 mg/kg body weight) topically once daily until the wounds had healed, whereas the control rats received no treatment. Findings indicated that on day 17, wounds treated with the extract fully closed compared to the control groups, which only saw an 85% contraction. Moreover, there were improvements in tensile strength, epithelialization, and wound size. The examination of the wounds at such a macroscopic scale revealed that the extract-treated groups needed a total of 17 days (for the non-diabetic group), twenty-two days (for the diabetes group) to heal completely. The metabolic alterations brought on by diabetes mellitus in connective tissue cause a delay in wound healing in diabetic individuals. Yet, the following illustrates an article, treatment with *A. squamosa* was shown to dramatically improve wounds from both incisions and excisions (Dwivedi et al., 2024). Its ability to promote wound contraction and collagen synthesis has been linked to its high phenol content.

Figure 5. *Annona squamosa* (Elanthamilan & Wang, 2025)

Catharanthus roseus (Nayak & Pinto Pereira, 2006)

C. roseus, which is sometimes called *Vinca rosea* L., *Lochnera rosea* (L.) Reichenb, and *Ammocallis rosea* (L.) Small, is a plant with white or purple blooms that originates from Madagascar. Different phytochemicals are found throughout various parts of the plant. This has been linked to the plant's ability to lower blood sugar (Mishra & Verma, 2017). *C. roseus* is considered an antihyperglycemic plant because it enhances glucose oxidation and glycolysis (through the Shunt pathway). After 60 days of therapy, diabetic rats treated in a study showed a 77.7% drop in blood glucose levels. Observations showed a reduction in lipid peroxidation, a key factor in diabetes complications, and an increase in glucose-metabolizing enzyme activity, confirming these results (Singh et al., 2014). Ethanol extract of *C. roseus* affected wound healing in diabetic rats. The present methods for the treatment of persistent diabetic wounds, including antibiotics, tissue grafts, corticosteroids, proteolytic enzymes, irrigation, debridement, some of these treatments can have adverse effects, which prompted this investigation 100 g of Water was used to clean and then dry the leaves of *C. roseus*. crushed into a solution with ethanol, 200 millilitres. The solution was filtered, and the research employed a clear solution. Sprague-Dawley female rats, healthy and weighing 180–200 g, were divided into five groups. STZ (50 milligrammes per kilogramme of body weight) was administered intraperitoneally in a single dosage to the animals in Groups 3, 4, and 5. Rats were anesthetized with intravenous amitriptyline hydrochloride (10 mg/kg), and the wound site was marked with methylene blue on their backs. With a surgical blade, sharp scissors, and toothed forceps, the excision incision was fully constructed, measuring 2.5 cm in together with 0.2 cm in depth. An extract was topically applied to Groups 2 and 4's wounds for 10 days in a single layer thickness. After surgery, the granulation tissue that had grown was removed, and the wet weight was measured. Topical application of the extract (Group 4) significantly accelerated wound contraction compared to diabetes and standard controls (Groups 3 and 1). Granulation tissue was multiplied, demonstrating a considerable rise in dry weight throughout the experimental diabetes group as compared to the animals in the control test group. Animals given the extract also showed rapid collagen breakdown. Animals not given *C. roseus* extract display wounds that are hard and crusty (Saravanan et al., 2021).

Due to their astringent and antimicrobial properties, which may be responsible for wound it is thought that *C. roseus* compounds, such as alkaloids, triterpenoids, including tannins, played a significant role in the wound healing process in diabetic rats (Nayak et al., 2007).

Figure 6. *Catharanthus roseus*

Centella asiatica (Diniz et al., 2023)

Traditional Chinese, traditional African medicine, and Ayurvedic remedy all use *Centella asiatica* as a therapeutic herb. It has been shown that it stimulates collagen production and fibroblast proliferation (Arribas-López et al., 2022). On the third day after inducing diabetes, excision wounds were produced rats had skin on the dorsal flank shaved, and excisional wounds were created under general anaesthesia by removing a 15 × 15 mm skin fragment. *C. asiatica* demonstrated potential to accelerate healing of diabetic wounds in animals; further research is needed to identify the active parts responsible (Shukla et al., 2019).

Figure 7. *Centella asiatica*

Acalypha langiana (Bharathy & Thanikachalam, 2024)

A. langiana is a wild herb whose leaves contain compounds used in traditional medicine for wound healing (Bharathy & Thanikachalam, 2024). The authors of this research used the water-based extract from fresh *A. langiana* leaves. STZ was administered once to induce diabetes. Two different kinds of wounds (excision and incision wounds) were produced on rats with blood sugar >250 mg/dL on day 7 post-diabetes induction. Topical application of *A. langiana* aqueous leaf extract significantly improved wound healing in a dose-dependent manner. In particular, the extract substantially increased tensile strength of incision wounds and accelerated tissue regeneration in granulation tissue compared to controls.

Figure 8. *Acalypha langiana*

Hylocereus undatus (Perez et al., 2005)

This plant, common in Brazil, has large, fragrant flowers that bloom at night and is used in traditional medicine and cuisine. Particularly, its flowers and leaves are used as hypoglycemic agents (Perez et al., 2005). The plant's leaves, flowers, and fruit extracts were used to evaluate wound healing (Mande et al., 2023). Wistar rats (male and female, 170–200 g) were used STZ (50 mg/kg) was administered intraperitoneally to induce diabetes. Each rat had one excision made by removing 500 mm of fully developed skin from a designated location on its back. Topical administration of the plant extract to diabetic rats significantly accelerated the healing process. Compared to the control, treatment of wounds with 0.5% solutions of leaves and flowers extracts in diabetic rats had a significantly higher tensile strength. In addition, granulation tissues from wounds treated with the flower extract showed a significant increase in collagen compared to the control treatment The research showed that the topical application of infusions of both leaf and flower extracts resulted in considerable wound-repair effects.

Figure 9. *Hylocereus undatus*

Punica granatum (Zekavat et al., 2016)

P. granatum flowers are widely used in the Middle East for wound healing and antimicrobial purposes. Male Wistar rats were used in their tests to find out if the plant could help heal wounds. After 15 hours of fasting, alloxan monohydrate (125 mg/kg), was administered into the peritoneum of each animal. Glucose-fed rats with glucose levels over 250 mg/dL had wounds inflicted on them after glucose was detected in order to determine whether the animals were diabetic (Zekavat et al., 2016). The following groups of animals were formed. Group 1: Healthy rats were given a basic ointment as a control; Group 2: Diabetic rats were given a basic ointment as a comparison; Groups 3 and 4: Rats were given a basic ointment prepared with 0.2% extracts; Group 5: Rats were given the common medication nitrofurazone. *P. granatum* extract enhanced wound healing and tissue regeneration compared to controls, observed on day 9 and day 18.

Figure 10. *Punica granatum*

Aloe vera (Chithra et al., 1998)

A. vera has been traditionally used worldwide to treat various ailments. It has glucose-lowering, anti-inflammatory, and antibacterial properties (Muslim et al., 2025). In an *in vivo* study, the capacity of a plant extract for wound healing was gauged using male Wistar rats. On day 7 after the induction of STZ-induced diabetes, sores developed. Excision and incision wounds were created and each type of wound was treated with *A. vera* extract for a set number of days. The pace of wound contraction was measured by drawing the excisions on clear paper with a millimetre scale, and the proportion of the wound that had healed was used to compute the change in wound size. The number of days it took for the wound to fully epithelialise was used to represent the epithelialisation time. Granulation tissue with a sharp rise in collagen content appeared on day 4. In mice given plant extract treatment, there was an increase in both protein and DNA content in the granulation tissue. The study concludes that *A. vera* extract accelerates wound healing in diabetic conditions and suggests that *A. vera* therapy could positively impact the various stages of wound recovery, including collagen contraction and fibroplasia, resulting in faster healing compared to untreated animals (Hashemi et al., 2015).

Figure 11. *Aloe vera*

Martynia annua (Lodhi and Singhai, 2013)

This annual plant, which has glandular hairs, is primarily used to treat epilepsy and tuberculosis. It is also used to treat inflammation, wounds and sore throats (Maenthaisong et al., 2007). The previously described approach was used to collect, identify and prepare the plant's leaves. Once STZ-induced diabetes had been induced in Wistar rats, an excision wound developed. Comparing the wounds in the experimental group with extract-treated wounds showed that they had significantly contracted. Furthermore, the hydroxyproline level in animals given plant extract was shown to be much greater than in the control group. Histological examination of mice given *M. annua* extract revealed an increased number of fibroblast cells and well-organised collagen fibres.

Figure 12. *Martynia annua*

Diabetes wound healing: The mechanism of action of medicinal herbs and their active components

There are four overlapping phases in which the functions of cells and metabolic reactions are involved in wound healing: homeostasis (coagulation prevents inflammation (invasion of macrophages and proteases to eliminate debris and pathogens, production of growth factors, and pro-inflammatory cytokines) (0-3 days); proliferation (cell migration, extracellular matrix development, granulation) tissue formation, and the development of granulation tissue) (Zhao et al., 2016). The duration of these overlapping wound healing stages is disrupted in diabetic individuals. Diabetes patients have a decreased ability to metabolise hyperglycemia as a consequence of situations involving excess glucose that impede wound healing (Puri et al., 1994). Modifications to the outer layer of red blood cells, including blood vessel constriction caused by hemoglobin glycation-induced hypoxia, further reduce the delivery of nutrients and oxygen to tissues (Obeagu, 2024). Wound healing in diabetes is markedly slowed by microvascular complications that lead to local ischemia. Blood glucose levels above 150 mg/dL impair immune system function, resulting in chronic inflammation. The main factors that interfere with the healing of diabetic wounds are microvascular issues, irregular inflammatory responses, poor angiogenesis, oxidative stress, reduced nitric oxide, poor keratinocyte and fibroblast migration and proliferation, and abnormal levels of matrix metalloproteinases (Kunkemoeller & Kyriakides, 2017).

The active ingredients in herbal products and their various modes of action have an impact on both biochemical and cellular mechanisms taking place throughout the various stages of wound recovery (Figure 13).

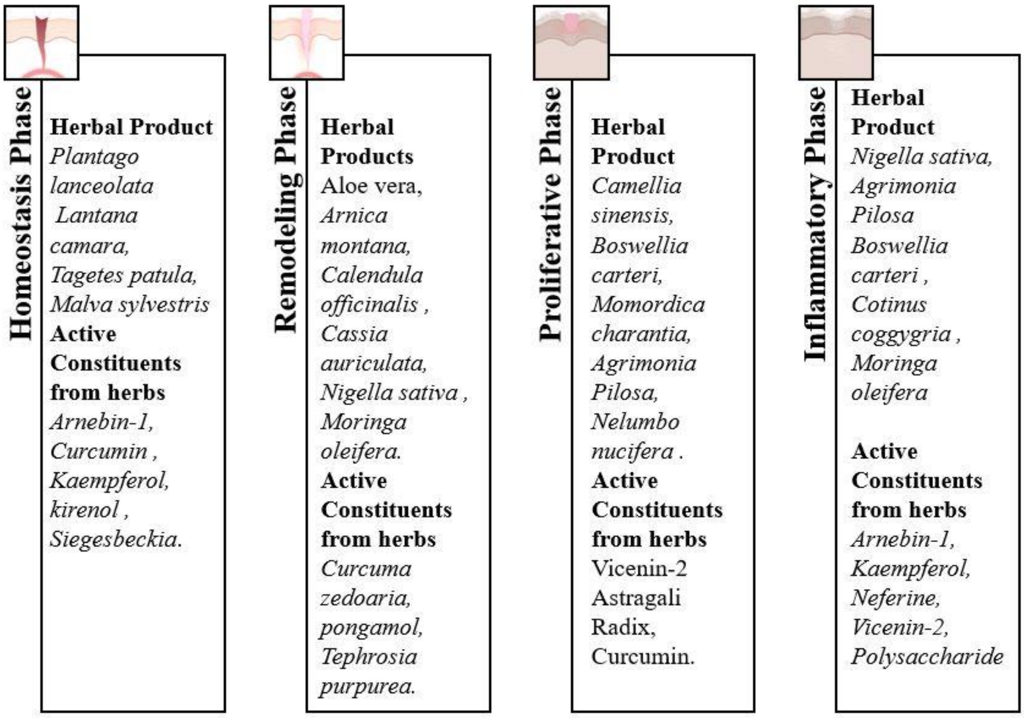

Figure 13. The effects of herbal supplements and their active ingredients on the stages of healing of diabetic wounds (Herman & Herman, 2023)

Oxidative stress and free radicals

High levels of reactive oxygen species (ROS), reactive nitrogen species (the renal system), and possibly free radicals throughout the body are the primary cause of oxidative stress. The antioxidant mechanism protects the body from the harmful effects of oxidative stress. It consists of major enzymes that eliminate ROS, including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). An imbalance between antioxidants and free radicals results in the overproduction of ROS, which damages cells and tissues and causes inflammation, neuropathy, ischemic lesions, and topical infections all of which slow the healing of diabetic wounds. Antioxidative mechanisms may thus enhance diabetic wound healing by reducing ROS levels. It is generally known that herbal remedies and their active ingredients have antioxidant properties (Singh et al., 2017). For example, Annona squamosa ethanolic extract increased both enzymatic and non-enzymatic antioxidants in wound tissues, improving wound healing in both healthy and diabetic rats. An ointment containing 0.5% (w/w) flavonoid fraction and 0.5% luteolin extracted from *Martynia annua*, as well as formulations with microparticles and dermal matrices impregnated with resveratrol, promoted diabetic wound recovery by enhancing free radical scavenging. Similarly, diabetic wounds that were left untreated, piper betel paste dramatically reduced the expression of Indicators of oxidative stress include SOD and 11b-HSD-1 (11b-hydroxysteroid dehydrogenase type 1). Apigenin species *Morus alba*, when combined with a hydrogel, significantly accelerated diabetic wound healing by increasing SOD and CAT levels in granuloma tissue. Similarly, flavonoid-rich extracts of *Tephrosia purpurea* ointment improved diabetic wound healing by raising levels of SOD, CAT, and GSH (Saini et al., 2016). Hydrogels containing 4% (w/w) *Blechnum orientale* extract had better antioxidant activity than standard agents (ascorbic acid, tocopherol, butylhydroxytoluen (BHT) as butyl hydroxytoluen, and Trolox-C as an analogue of vitamin E), and they were also successful in treating diabetic ulcer wounds. A mixture of *Cotinus coggygria* ointments, *Quercus infectoria* preparations, ethanol extracts of *Salvia kronenburgii* combined with *Salvia euphratica* ointment, kaempferol ointments, and a herbal combination containing *Cassia auriculata*, *Mangifera indica*, *Ficus* *benghalensis*, and *Cinnamomum tamala* has also been reported to promote wound healing (Aboelsoud, 2010).

Reduced immune response of inflammatory cells

Due to macrophage-mediated inflammation, increased glucose levels, and elevated free fatty acids, diabetes leads to the production of more pro-inflammatory cytokines (Bhowmik et al., 2013). During the proliferative stage of diabetic wound healing, anti-inflammatory M2-like macrophages are predominant, whereas pro-inflammatory M1-like macrophages produce various cytokines, including IL-12, IL-1, IL-6, TNF, and iNOS. These cytokines recruit macrophages and immune cells, which are essential for proper wound healing in diabetes. It has been shown that IL-1 produced by macrophages and dysregulation of macrophages cause prolonged inflammation and delayed wound healing in diabetic patients (Mirza et al., 2014).

Herbal products and their active ingredients with anti-inflammatory properties support diabetic wound healing and help manage its complications. Compared to mupirocin as a positive control, topical ointments containing *Aloe vera* gel and *Teucrium polium* hydroethanolic extracts shortened the inflammatory phase and reduced tissue levels of malondialdehyde (MDA), TNF, and IL-1. Through the overexpression of VEGF and regulation of inflammatory mediators (TNF, IL-1, IL-6, iNOS synthase, and COX-2), *Moringa oleifera* enhanced wound contraction. *Solanum xanthocarpum* gel reduced levels of pro-inflammatory cytokines (IL-1, IL-6, and TNF) while increasing VEGF levels. Kirenol derived from *Siegesbeckia orientalis* promoted wound closure by lowering NF-κB, iNOS, MMP-2, MMP-9, and COX-2 levels. Extracts of *Lithospermum radix* and curcumin-loaded bilayer nanofibrous scaffolds reduced IL-6 and TNF, demonstrating their anti-inflammatory effects. Neferine, a compound from lotus (*Nelumbo nucifera*), facilitated healing by upregulating growth factors (GFs) and downregulating inflammatory mediators (NF-κB, TNF, IL-1, IL-8, iNOS, and COX-2). Through the NF-B pathway, vicenin-2 hydrocolloid films decreased levels of cytokines that promote inflammation (IL-1, IL-6, and TNF) as well as mediators (iNOS and COX-2), and NO. In addition, *Quercus infectoria* extract applied to diabetic mouse wounds decreased IL-1 and TNF production, two key pro-inflammatory cytokines produced by macrophages and monocytes (Raina et al., 2008).

Decreased production of growth factors

Growth factors are required to initiate and maintain the different stages of wound healing. Several growth factors are released at the wound site, playing a crucial role in the wound healing process. These include transforming growth factor (TGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). These molecules are essential for regulating cell proliferation, migration, angiogenesis, and tissue regeneration during wound repair. TGFs attract and encourage the activation of immune cells such as neutrophils, macrophages, and lymphocytes, along with keratinocytes and fibroblasts, and also stimulate the development of other growth factors (Tavakoli et al., 2022). Diabetes-related wounds have been shown to have lower TGF concentrations. In diabetic foot ulcers, EGF has been linked to a systemic reduction in pro-inflammatory markers and antioxidant effects. Moreover, EGF increases fibroblast replication, collagen production, re-epithelialization, and all of which accelerate wound healing. By activating growth factors, several herbal remedies and their active ingredients promote cell migration, proliferation, and contraction in diabetic wounds. By promoting vigorous TGF expression, *Momordica charantia* accelerated wound healing. Expression of VEGF, IGF-1, GLUT-1, and FGF-2 was markedly elevated by a formulation combining *Aloe vera* gel and *Teucrium polium* extract in an ointment. Arnebin-1 derived from *Arnebia euchroma*, 20(S)-protopanaxadiol obtained from *Panax notoginseng*, and *Stryphnodendron adstringens* gel have all been shown to accelerate wound healing and enhance VEGF expression. Vicenin-2 further improved healing under hyperglycemic conditions by stimulating VEGF and TGF pathways, thereby supporting cell proliferation, migration, and wound contraction (Herman & Herman, 2023).

Migratory and proliferative defects in keratinocytes and fibroblasts

At the proliferative stage, endothelium cells, the main component of wound healing, and keratinocytes, the epidermal skin cells, vascular cells, and fibroblasts (the main type of cell in connective tissues) divide, move, and change into different types of cells. This allows granulation tissue to form, the dermal matrix to be rebuilt, surface integrity to be restored, and the wound to close. Herbal items and their active ingredients may promote these processes. By promoting fibroblast proliferation and collagen deposition, ointments containing *Teucrium polium* or *Aloe vera*, used either alone or in combination, accelerated wound healing in diabetic models. Topical management of *Hypericum perforatum* in olive oil demonstrated considerably greater collagen density, higher hydroxyproline tissue levels and increased tensile strength compared to the control group. By promoting collagen production and fibroblast proliferation, *Hypericum perforatum* gel promoted tissue regeneration. An extract from *Camellia sinensis* promoted the synthesis of collagen and fibronectin. Re-epithelialization, increased fibroblast proliferation, and increased collagen synthesis were all observed with *Blechnum orientale* hydrogel (Herman & Herman, 2023).

Curcumin, derived from *Curcuma longa*, is used to produce electrospun nanofibers, accelerating wound healing in regions of well-formed granulation tissue that are characterized by rapid epithelial regrowth, collagen deposition, fibroblast proliferation, and the development of sweat gland and hair follicle tissues (Ranjbar-Mohammadi et al., 2016). Collagen production, wound healing, and epidermal and appendage differentiation were all accelerated by *Astragalus radix* polysaccharide loading on tissue engineering scaffolds (Yang et al., 2015).

Ineffective angiogenesis

An important part of how a wound heals is angiogenesis, also called neovascularization. This is when a new capillary network (microvasculature) forms as a result of low oxygen levels or other stimuli because of the lack of oxygen caused by diabetes, macrophages release angiogenesis-related factors such as TGF and IL-1. Among the most significant angiogenic factors are VEGF molecules, whose production is triggered by hypoxia and high blood sugar. Hyperglycemia activates the transcription factor HIF-1, which upregulates target genes such as VEGF-A to promote angiogenesis in response to injury-induced hypoxia. Hyperglycemia also causes TGF-mediated indirect VEGF overexpression (Panche et al., 2016). Also, in diabetic mice, elevated levels of FGF and PDGF were also found to promote wound healing and were associated with angiogenesis. Weak vascular networks are closely linked to chronic wounds that don't heal, which are caused by diabetes. Herbal remedies and their primary ingredients contain potential angio-modulators that influence the angiogenesis process during diabetic wound healing (Yong et al., 2024). *Camellia sinensis* extract speeds up the process of angiogenesis and vascular remodelling (Hajiaghaalipour et al., 2013). *Astragali radix* polysaccharides facilitated the regeneration of cutaneous microcirculation when delivered through tissue-engineering scaffolds (Yang et al, 2015). Several bioactive compounds were shown to impact vascularization and angiogenesis in diabetic wounds, for example curcumin from *Curcuma longa* incorporated into electrospun (Ranjbar-Mohammadi et al., 2016).

Future insights

Using medicinal herbs to treat diabetic wounds holds significant promise, yet several challenges must be addressed before these natural therapies can become a standard part of modern medical practice. Future research should prioritize key areas such as phytochemical standardization, advanced drug delivery systems, mechanistic studies, clinical validation, and regulatory approvals to enhance the effectiveness of herbal medicine in wound care.

One major hurdle in herbal medicine is the lack of consistency in phytochemical composition and quality control. The concentration levels of bioactive compounds in medicinal plants can vary widely due to differences in plant species, geographical origin, harvesting conditions, and extraction methods. To ensure reliable therapeutic effects, sophisticated analytical methods, such as HPLC, mass spectrometry, and NMR spectroscopy, should be utilized for precise quantification and standardization of plant extracts. Establishing stringent quality control methods will improve the reliability and reproducibility of herbal-based treatments.

Understanding the molecular mechanisms behind medicinal plants' wound-healing properties is another crucial area of focus. While many bioactive compounds have demonstrated effectiveness in preclinical studies, their specific mechanisms that operate at the cellular and molecular level remain largely unknown. Future studies should explore how these compounds influence key biological pathways, including oxidative stress modulation, inflammatory cytokine regulation, fibroblast proliferation, and extracellular matrix remodeling. Advanced omics technologies, including genomes, proteomics, and metabolomics, can provide deeper insights into the pharmacodynamics of herbal compounds, making room for greater concentration and personalised wound care strategies.

Nanotechnology-based herbal formulations offer an exciting opportunity to enhance the therapeutic efficacy of medicinal plants. Many phytochemicals suffer from poor solubility and rapid degradation in the body, limiting their bioavailability and effectiveness. Nanocarrier-based delivery systems, including nanoemulsions, liposomes, polymeric nanoparticles, and hydrogels, can enhance the stability, controlled release, and precise deliver of herbal compounds to wound sites. Future research should explore these innovative nano-formulations to optimize wound-healing outcomes in diabetic patients (Qin et al., 2022).

Despite promising preclinical findings, large-scale clinical studies are critical for validating the safety, and efficacy, of herbal treatments for diabetic wound healing. Well-structured randomized controlled trials (RCTs) should be conducted to determine the best dose, treatment duration, which stem and potential side effects of herbal therapies in human subjects. Additionally, fostering interdisciplinary collaboration between traditional medicine practitioners, biomedical researchers, and clinicians can help bridge the gap between herbal medicine and evidence-based clinical practice, facilitating its integration into conventional healthcare.

Regulatory approval remains a key barrier to the widespread adoption of herbal medicine in mainstream healthcare. To gain global acceptance, medicinal plants must undergo rigorous evaluation under standardized regulatory frameworks established by authorities such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organisation. Establishing guidelines for approval, safety assessment, and labeling of herbal wound-healing products will enhance their credibility and integration into modern medical practice. Furthermore, healthcare policies should encourage the use of herbal medicine alongside conventional treatments, promoting a more holistic and patient-centered approach to wound care. Sustainability is another critical aspect of future research in herbal medicine. As the demand for medicinal plants continues to rise, overharvesting and environmental degradation threaten many species. Sustainable agricultural practices, plant tissue culture techniques, and metabolic engineering can help ensure the large-scale production of bioactive compounds while preserving biodiversity. Governments, researchers, and policymakers must work together to promote sustainable harvesting methods and conservation initiatives.

Artificial intelligence (AI) and computational drug discovery also offer exciting possibilities for accelerating the identification of medicinal plants and their active compounds for wound healing. AI-driven bioinformatics tools can predict the pharmacological properties of herbal compounds, allowing for a more targeted and efficient drug discovery process. By combining AI with traditional herbal research, scientists can identify and optimize novel wound-healing agents with greater precision. The future of diabetic wound healing lies in a multidisciplinary approach that integrates traditional botanical knowledge with cutting-edge scientific advancements. By addressing challenges related to phytochemical standardization, drug delivery, clinical validation, regulatory frameworks, and sustainability, medicinal plants can be transformed into reliable and effective therapeutic options. With continued research, technological innovation, and a commitment to sustainability, herbal medicine has the capacity to revolutionise diabetic wound care and enhance the lives of millions of people worldwide.

Conclusion

Managing wounds caused by diabetes remains a significant concern in modern medicine, demanding innovative and effective treatment approaches. Medicinal plants, packed with bioactive compounds, have emerged as a viable alternative to traditional wound-care methods. Research has shown that phytochemicals such as flavonoids, alkaloids, terpenoids, and polyphenols play a crucial part in wound recovery by boosting blood vessel formation, reducing oxidative stress, regulating inflammation, and stimulating collagen production.

Although traditional healing systems have long endorsed the use of herbal remedies for treating wounds, modern scientific studies have increasingly validated their efficacy and mechanisms of action. However, despite encouraging findings from preclinical and some clinical studies, challenges remain, particularly regarding standardization, bioavailability, and regulatory approval. To fully harness the potential of these herbal interventions, more extensive research, including well-structured clinical trials, is needed to confirm their safety and effectiveness.

Incorporating medicinal plants into mainstream diabetic wound care could transform treatment strategies, providing cost-effective, natural, and patient-friendly solutions. By bridging the gap between traditional healing wisdom and modern scientific advancements, we can unlock new phytotherapeutic approaches for diabetic wound healing, ultimately improving patient outcomes and easing the burden on healthcare systems worldwide.

Author contributions

This two-author article was carried out and prepared by both authors: PS, AP.

Declaration of interests

The authors declare no conflict of interest.

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