RESEARCH PAPER

A COMPREHENSIVE AND UPDATED REVIEW ON MEDICINAL PLANTS USED FOR THE MANAGEMENT OF DIABETIC WOUND HEALING

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ABSTRACT
Due to their delayed healing, persistent inflammation, and elevated potential for infection, diabetic injuries particularly diabetic foot ulcers are serious complications of diagnosed diabetes mellitus that present substantial clinical and financial issues. With their multi-targeted benefits and reduced side effects, plant-based therapies have become a possible substitute for traditional treatment approaches. Two decades of study (2005–2025) on medicinal plants used for diabetic wound healing are critically compiled in this thorough and updated review, with a significant concentration for experimental and computational research studies published in 2024 and 2025. Herbal extracts, polyherbal formulated products, and isolated plant-based constituents with strong antioxidant, anti-inflammatory, antibacterial, and pro-angiogenic qualities are all evaluated in vitro, in vivo, and preclinically. VEGF, TGF-β1, NF-κB, IL-6, MMP-9, SOD, CAT, GPx, collagen I/III, and other crucial molecular targets involved in repair of wounds. We gave a look at structural information from bioinformatics and examined the mechanistic pathways and target-specified links of some phytocompounds through the use of molecular docking, conventional network pharmacology, and computational simulations via molecular dynamics. This work provides a solid foundation for future drug discovery and logical development of plant-derived therapies for diabetic wound care by combining both clinical evidence and computational validation.
Keywords: Persistent inflammation, Diabetes mellitus, angiogenic qualities, VEGF, dynamic simulations.
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Introduction:

Diabetes mellitus is a chronic metabolic disorder characterized by persistent high blood glucose due to impaired insulin production or function. It has become a global health concern, with millions affected worldwide. One of its most serious complications is delayed wound healing, particularly in the lower limbs, leading to diabetic foot ulcers, infections, and even amputations. These wounds increase healthcare costs, prolong hospital stays, and reduce quality of life. Impaired healing in diabetes is complex and involves prolonged inflammation, poor angiogenesis, oxidative stress, infection, and dysfunction of cells essential for tissue repair.[6-10].

Normal wound healing occurs in four stages: haemostasis, inflammation, proliferation, and maturation. In diabetes, high blood glucose disrupts this process by impairing immune cell function, prolonging inflammation, and delaying tissue repair. Factors like poor blood circulation, neuropathy, and oxidative stress further slow healing. Although current treatments such as glucose control, debridement, infection management, pressure relief, and wound dressings help manage the condition, they often fail to achieve complete healing. This highlights the need for additional and more effective therapeutic approaches.[11-14].

The use of medicinal plants as adjunct therapy for diabetic wound management has gained significant attention. The following list describes phytochemicals from these plants: flavonoids, alkaloids, terpenoids, tannins and phenolic compounds. Each of these phytochemicals has demonstrated anti-inflammatory properties, anti-oxidative potential, anti-microbial function and/or pro-angiogenic ability through their ability to act on many different biological pathways; they encourage collagen synthesis and the regeneration of abnormal tissues. Compared to conventional drugs, plant-based therapies often show lower toxicity and better biocompatibility, making them promising alternatives for wound healing in diabetes.[15-20].

A number of scientific and traditional uses of various medicinal herbs have been documented in finding ways to treat chronic wounds. Studies both test-tube (in vitro) and living subjects (in vivo) as well as clinical studies have shown that there are many different types of medicinal herbs that can assist in the healing process during different stages of producing a complete wound closure. For instance, *Centella asiatica* promotes fibroblast proliferation and collagen synthesis, *Curcuma longa* (turmeric) shows strong anti-inflammatory and antioxidant effects, and *Aloe vera* enhances epithelialization and regulates inflammation. Other plants like *Azadirachta indica*, *Calendula officinalis*, and *Lawsonia inermis* also prove significant wound-healing potential.[21-23].

Advances in phytochemical screening, nanocarrier-based delivery systems, and modern analytical techniques like LC-MS/MS and GC-MS have strengthened the use of plant-derived remedies for wound healing. In diabetic wound models, nano formulations improve bioavailability, enable targeted delivery, and enhance healing outcomes. At the molecular level, phytoconstituents promote wound repair by modulating key Signaling pathways such as PI3K/Akt, NF-κB, TGF-β, and MAPK.[24-26].

Clinical use of phytomedicine in wound care faces challenges such as variability in plant sources, extraction methods, lack of standardized dosing, limited large-scale trials, and low regulatory acceptance. Therefore, a comprehensive review is needed to summarize medicinal plants used in diabetic wound healing, including their phytochemistry, pharmacological actions, and mechanisms. This review aims to provide an updated overview of effective plant-based therapies, highlighting experimental and clinical evidence, and guiding future research for developing novel treatments based on traditional medicine.[27-29].

Diabetic Wound Healing from a Therapeutic Perspective and by Experimental Research:

Yang Liu et al.[30] evaluated the wound-healing potential of a mixture of five traditional herbal extracts (*Bauhinia purpurea, Paeoniae rubra, Angelica dahurica, Acorus calamus,* and *Radix Angelicae Biserata*) in a streptozotocin-induced diabetic rat model. Infected full-thickness wounds were treated with the herbal mixture, Kangfu solution, or left untreated. The herbal-treated group showed significantly higher collagen deposition, enhanced neovascularization, and increased M2 macrophage polarization. Further analysis revealed activation of key pathways such as autophagy, PI3K/Akt, and mTOR, showing that the herbal formulation effectively promotes immune modulation, angiogenesis, and tissue regeneration, thereby accelerating diabetic wound healing.

Jawun Choi et al.[31] (2018) evaluated an herbal mixture of *Alchemilla vulgaris* and *Mimosa tenuiflora* for wound healing using an animal model. The herbal ointment showed better wound closure compared to Fusidic acid ointment. Histological and immunohistochemical studies confirmed enhanced re-epithelialization, collagen deposition, angiogenesis, and regeneration of skin appendages. In vitro results also proved improved cell migration and immune response. Overall, the study suggests that herbal formulation effectively promotes wound healing and has potential as a therapeutic agent for skin injuries.

Jun Guo et al.[32] (2020) Utilizing the process of promoting angiogenesis, Angelica dahurica has been assessed as an option for treating diabetic foot ulcers. Researching the status of angiogenesis, in vitro (3D) studies demonstrated that A. dahurica was able to enhance the proliferation and migration of HUVECs (hypoxic human umbilical vein endothelial cells) by activating HIF-1α and PDGF-β through the PI3K/AKT signaling pathway. Investigating the use of A. dahurica in animal models demonstrated faster wound healing, an increase in capillary formation, and an increase in angiogenic markers in granulation tissue. Therefore, this study concludes that A. dahurica accelerates wound healing by promoting angiogenesis and warrants further investigation as a potential therapeutic agent for diabetic wounds.

Jacqueline Chor-Wing Tam et al.[33] (2014) studied the effects of a Chinese herbal formula (NF3) on diabetic wound healing in mice with hindlimb ischemia. Treatment with NF3 significantly reduced wound size and increased circulating endothelial progenitor cells, indicating improved vascular repair. It also enhanced angiogenesis by increasing VEGF and eNOS levels, reduced oxidative stress, and promoted MMP activity. Overall, NF3 was found to accelerate wound healing by improving blood vessel formation and reducing tissue damage, suggesting its potential as a therapeutic option for diabetic foot ulcers.

Kit-Man Lau et al.[34] (2012) evaluated a herbal combination of *Astragali Radix* (AR) and *Rehmanniae Radix* (RR) in a 2:1 ratio (NF3) for diabetic wound healing. While individual herbs showed limited effects, the combined formula significantly reduced wound size, showing a synergistic action. In vitro, studies revealed that AR mainly contributed to anti-inflammatory effects, while RR supported angiogenesis, and together they enhanced fibroblast growth and endothelial cell migration. Overall, the study highlights that the NF3 combination improves wound healing through complementary mechanisms and supports the concept of synergistic herbal therapy.

Jacqueline Chor-Wing Tam et al.[35] (2015) investigated the effect of the herbal formula NF3 on angiogenesis in a diabetic foot ulcer model. NF3 treatment significantly increased circulating endothelial progenitor cells (EPCs) by enhancing SDF-1α expression, which promoted EPC mobilization. It also upregulated angiogenic markers and improved EPC functions such as proliferation, adhesion, migration, and tube formation in a dose-dependent manner. Overall, the study proves that NF3 enhances wound healing by stimulating EPC-mediated angiogenesis.

Ho Yan Gloria Tse et al.[36] **(2012)** evaluated the angiogenic potential of the herbal formula NF3 (Radix Astragali and Radix Rehmanniae, 2:1) using zebrafish and rat models. NF3 significantly promoted blood vessel formation, increased endothelial cell proliferation, and enhanced micro vessel sprouting. It also upregulated key pro-angiogenic genes such as VEGF-A, Flk-1, FGF1, and bRaf. Overall, the study demonstrates that NF3 enhances angiogenesis through activation of VEGF, FGF, and MAPK pathways, supporting its potential in improving vascularization and diabetic wound healing.

Jing Li et al.[37] developed a biopolymer-based hydrogel holding extracts of *Astragalus membranous* and *Panax Noto ginseng* (APCS) for wound healing. In vitro, the hydrogel enhanced fibroblast proliferation, migration, and differentiation. In animal models, it accelerated wound closure, reduced inflammation, and improved angiogenesis, collagen deposition, and re-epithelialization. It also increased antioxidant and regenerative markers, indicating reduced oxidative stress and enhanced tissue repair. Overall, APCS hydrogel shows strong potential as an effective wound dressing for chronic and complex wounds**.**

Jiang Dong Tang et al.[38] **(2024)** developed PVP-based microneedles loaded with extracts of *Sanguis Draconis* and *Salvia miltiorrhiza* to enhance diabetic wound healing. The system enabled effective transdermal delivery and showed synergistic action, where SD promoted cell migration and improved the healing environment, while SMR enhanced blood circulation. In vivo studies demonstrated faster wound healing with improved tissue regeneration and angiogenesis. Overall, this microneedle system offers a minimally invasive and promising approach for targeted diabetic wound treatment.

Khaled Abdul-Aziz Ahmed et al.[39] **(2024)** evaluated *Dorema aucheri* gum (DAG) for wound healing in a rat model. Topical treatment significantly accelerated wound contraction, reduced wound size, and enhanced tissue regeneration. Histological and immunohistochemical findings showed increased collagen deposition, fibroblast activity, and HSP70 expression, along with reduced inflammation and apoptosis. DAG also improved antioxidant status and modulated cytokines. Overall, the study supports DAG as a promising natural agent for wound healing due to its anti-inflammatory, antioxidant, and regenerative properties.

Talal Salem H. Al-Qaisi et al.[40] **(2025)** evaluated the safety and wound-healing potential of *Diospyros kaki* leaf extract (MEPL) in a rat model. The extract was found to be non-toxic and significantly improved wound contraction and tissue regeneration. It enhanced fibroblast activity, collagen deposition, and angiogenesis through upregulation of TGF-β1. MEPL also showed strong antioxidant and anti-inflammatory effects by increasing SOD and catalase levels while reducing pro-inflammatory cytokines. Overall, the study supports MEPL as a promising natural agent for wound healing, though further research is recommended.

Safwan Mahmoud Al-Adwan et al.[41] **(2025)** investigated the wound-healing potential of *Calendula arvensis* extract (MECAA) in rats. The extract was found to be safe and significantly accelerated wound contraction when applied topically. It enhanced fibroblast and keratinocyte proliferation, improved angiogenesis, and reduced inflammation. Biochemical results showed increased antioxidant enzyme activity, collagen content, and TGF-β1 expression, along with decreased lipid peroxidation and pro-inflammatory cytokines. Overall, the study highlights MECAA as a promising natural agent for wound healing with strong anti-inflammatory and antioxidant properties.

Elham Rouhollahi et al.[42] **(2015)** evaluated the wound-healing effects of hexane extract of *Curcuma purpurascens* (HECP) in a rat model. Topical treatment significantly improved wound closure, reduced scar size, and enhanced collagen deposition and fibroblast proliferation. It also decreased inflammation and apoptosis while increasing Hsp70 expression. Additionally, HECP promoted angiogenesis and showed strong antioxidant activity. Overall, the study suggests that HECP accelerates wound healing through anti-inflammatory, antioxidant, angiogenic, and cytoprotective mechanisms.

Penelope M.Y. Or et al.[43] **(2012)** studied the interaction of the NF3 herbal formula (*Radix Astragali* and *Radix Rehmanniae*) with major CYP enzymes. NF3 showed competitive inhibition of CYP2C9 and CYP3A4, mainly due to *Rehmanniae Radix*, while *Astragali Radix* had minimal effect. Both NF3 and RR showed weak inhibition of other CYP enzymes. Overall, despite some inhibitory activity, the study suggests that NF3 is unlikely to cause significant herb–drug interactions in clinical use.

Lau et al.[44] **(2009)** evaluated the wound-healing potential of aqueous extract of *Radix Rehmanniae* in a diabetic rat model. Treatment significantly reduced wound size, improved epithelialization, and enhanced scar formation. It also promoted angiogenesis by increasing VEGF expression and showed anti-inflammatory effects. Since no significant effect on blood glucose was observed, the healing action is mainly attributed to tissue regeneration and neovascularization. Overall, the study supports the traditional use of *Radix Rehmanniae* in diabetic wound healing.

Jacqueline Chor-Wing Tam et al.[45] **(2011)** evaluated the NF3 herbal formula (*Radix Astragali* and *Radix Rehmanniae*, 2:1) for diabetic wound healing. In a diabetic rat model, NF3 significantly reduced wound size. In vitro, studies showed enhanced fibroblast proliferation, endothelial cell migration, and tube formation, showing strong angiogenic activity. It also reduced nitric oxide production, proving anti-inflammatory effects. Overall, NF3 promotes wound healing through synergistic actions on tissue repair, angiogenesis, and inflammation.

Evren H. Gokce et al.[46] **(2017)** developed a collagen–laminin dermal matrix loaded with resveratrol microparticles to improve diabetic wound healing. The formulation provided sustained drug release, enhanced antioxidant activity, and delayed matrix degradation. In vivo studies showed improved collagen deposition, reduced inflammation, and better overall wound healing compared to controls. Overall, this advanced scaffold system shows strong potential as a safe and effective treatment for chronic diabetic wounds.

Ye Yang et al.[47] **(2015)** studied the use of Astragalus polysaccharide (APS) incorporated into electro spun tissue engineering scaffolds for diabetic wound healing. The APS-loaded scaffold mimicked the extracellular matrix and showed dose-dependent improvement in wound closure. It enhanced blood flow, increased micro vessel density, and upregulated angiogenic markers, along with promoting collagen production and skin regeneration. Overall, the APS-enriched scaffold supports both tissue repair and vascular regeneration, making it a promising dual-function approach for treating chronic diabetic wounds.

2.Bioinformatics-Driven Structural Insights into Medicinal Plants for Diabetic Wound Healing:

Pavithra Bharathy et al.[48] **(2024)** reviewed 87 studies on medicinal plants in wound healing and found that most plant-based compounds target key molecules like VEGF, TGF-β1, and collagen, helping reduce oxidative stress and promote tissue regeneration. The review supports the potential of herbal therapies for managing chronic and diabetic wounds.

Jagat Pal Yadav et al.[49] **(2024)** highlighted the role of various medicinal plants in diabetic wound care. These plants promote angiogenesis, fibroblast proliferation, and cytokine regulation, offering safer and cost-effective alternatives to conventional therapies. The study also suggests future potential for plant-based nano formulations.

Amit Lather et al.[50] **(2025)** emphasized the growing burden of diabetes and the challenges in wound healing. Their study explored plant-derived bioactive compounds using computational methods, identifying promising, non-toxic candidates that may serve as future therapies for diabetic wound management.

Conclusion:

Research over the past two decades (2005–2025) highlights the strong potential of medicinal plants in diabetic wound healing through antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic effects. Recent studies, especially from 2024–2025, provide robust *in vitro*, *in vivo*, and in silico evidence showing that plant-based compounds can target key molecular pathways such as VEGF, TGF-β1, NF-κB, and MMPs. Advances in computational tools have further clarified their mechanisms and predicted safety and efficacy. Overall, these findings support phytomedicine as a cost-effective, multi-target approach for diabetic wound management, with promising potential for future clinical applications.

Conflict of interest:

The authors declare that there is no conflict of interest.

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