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Innovative Strategies of Plant-Based Therapies in Diabetic Wound Healing: Mechanisms and Advances

S. Raghavi
Department of Biotechnology
Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India
https://orcid.org/0009-0005-9127-0675

S. Haritha
Assistant Professor, Department of Biotechnology
Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India

Mohamed Jameer Basha Jahankir
Research Associate, Caldor Health Technologies Private Limited, Coimbatore, Tamil Nadu, India

Abstract
Wound healing is a critical global health issue, significantly affecting patient outcomes and healthcare systems, particularly in developing countries with limited resources. Chronic wounds, especially diabetic ulcers, pose a serious challenge due to their prolonged healing time and high risk of complications. Herbal medicine is increasingly sought as an alternative or complementary treatment, driven by its affordability, accessibility, and minimal side effects. Medicinal plants are known to possess bioactive compounds that can enhance wound healing by targeting multiple biological pathways. Diabetes, a condition affecting over 530 million people in 2024, disrupts the natural wound-healing process through persistent hyperglycemia, which leads to poor circulation, impaired immune function, and elevated oxidative stress. Projections suggest that by 2050, the number of diabetic individuals will rise to 783 million, highlighting the urgent need for innovative and effective solutions to manage diabetic wounds. This paper will explore the factors affecting wound healing in diabetic patients, including glycemic control, vascular complications, and infection risks. It will also examine the mechanisms of action of medicinal plants, focusing on their role in promoting angiogenesis, reducing inflammation, and enhancing collagen synthesis. By discussing these aspects, this review aims to provide insights into the potential of medicinal plants as viable options for improving wound healing outcomes in diabetic patients.

Keywords: Diabetes, Wound-Healing, Chronic Wounds, Complications, Medicinal Plants, Collagen Synthesis

Introduction

Diabetes Mellitus (DM) is a long-term metabolic condition marked by consistently elevated blood glucose levels due to defects in insulin secretion or action. It encompasses various types, including Type 1, Type 2, and gestational diabetes, each with distinct pathophysiological mechanisms and risk factors. The global prevalence of DM is alarming, with projections indicating a rise from 382 million cases in 2013 to 592 million by 2035. Understanding the classification, complications, and management strategies is crucial for addressing this public health challenge. Diabetes mellitus is a complex metabolic disorder that can be classified into several types. Type 1 diabetes mellitus (DM) involves the autoimmune destruction of pancreatic beta cells, resulting in absolute insulin deficiency (Karabagli). In contrast, Type 2 diabetes mellitus is distinguished by the presence of insulin resistance and inadequate insulin secretion, often linked to obesity and lifestyle factors (Yameny). Another form, gestational diabetes mellitus,

occurs during pregnancy and increases the likelihood of developing Type 2 DM later in life (Karabagli). Uncontrolled diabetes can lead to severe Microvascular and macrovascular complications encompass conditions such as neuropathy, retinopathy and cardiovascular diseases (Yameny). Additionally, the condition is associated with a high prevalence of psychological disorders such as anxiety and depression, particularly among individuals with low income and education levels (Tamang). Effective management strategies encompass lifestyle interventions, such as diet and exercise, alongside pharmacological treatments, including insulin therapy, metformin, and GLP-1 receptor agonists (Yameny). Beyond glycemic control, addressing the psychological and socioeconomic dimensions of the disease is essential. Embracing a comprehensive approach can greatly improve patient outcomes and elevate their quality of life.

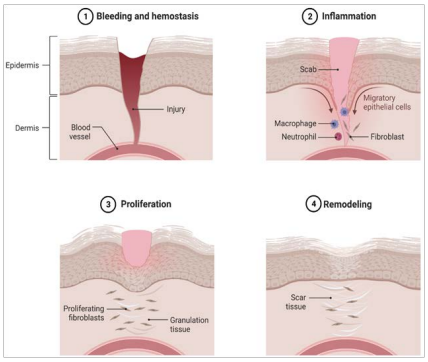

Figure 1 Stages of Wound Healing

Mechanism of Diabetic Wound-Healing

Homeostasis

Diabetic wound healing is a complex process divided into four phases: homeostasis, inflammation, proliferation, and remodeling (Figure 1). These phases are regulated by various genes and signaling pathways, including VEGF, TGF-β, and NF-κB, which are often dysregulated in diabetic wounds (Kamal et al.). The compound $1,25(OH)_2D_3$ has been demonstrated to enhance the healing process by modulating inflammation, restoring vascular endothelial function, and promoting angiogenesis via the PI3K/AKT/HIF-1α pathway (Ma et al.). Additionally, CD64, an IgG-binding Fcgr1 receptor, is crucial for diabetic wound healing, facilitating CD163+ M2 macrophage infiltration (Zhang et al.). Epigenetic mechanisms, including histone modifications, DNA methylation, and the regulation of noncoding RNAs, are crucial in modulating inflammation, angiogenesis, and cell differentiation throughout the healing process (Ju et al.). These findings highlight the importance of targeted interventions to address the dysregulation observed in diabetic wounds, paving the way for improved therapeutic approaches.

Inflammation

The proliferation phase of wound healing is significantly influenced by the interplay of inflammatory cytokines and neuropeptides within the wound microenvironment. Cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) play vital roles in regulating cellular responses, while neuropeptides like substance P (SP) and neuropeptide Y (NPY), secreted by peripheral nerves, are pivotal for tissue repair. In diabetic wounds, prolonged and unresolved inflammation disrupts the transition to the proliferation phase, impairing critical processes such as fibroblast activation, angiogenesis, and extracellular matrix deposition. Acute inflammation is essential for initiating cellular proliferation; however, chronic inflammation not only delays this phase but also predisposes tissue to complications such as fibrosis and cancer development. Additionally, extrinsic factors, including infections and external mechanical pressures, further contribute to delays in healing. Addressing both intrinsic and extrinsic factors is crucial to modulating inflammation, fostering proliferation, and achieving optimal wound healing outcomes.

Proliferation

Diabetic wound healing is impaired due to complex factors affecting various cell types and processes. Abnormal keratinocyte and fibroblast migration, proliferation, and differentiation contribute to delayed healing. Macrophage function is disrupted, leading to sustained inflammation and impaired transition to the proliferation phase. Enhanced proliferation of Ly6C+ monocytes/macrophages, driven by CCL2/CCR2 signaling, exacerbates chronic inflammation in diabetic wounds. Prolonged expression of

TNF-α also hinders healing (Xu et al.). Epigenetic mechanisms play a role in regulating macrophage plasticity and keratinocyte/fibroblast function during wound repair, with diabetes altering these epigenetic processes (den Dekker et al.). Novel treatments, such as low-intensity laser irradiation, show promise in improving diabetic wound healing by stimulating cell migration, viability, and proliferation, as well as increasing ATP production and providing anti-inflammatory effects (Houreld). Diabetic wound healing is impaired due to various cellular abnormalities. Bone marrow-derived progenitor cells show defective recruitment, survival, and proliferation at wound sites in diabetic mice (Albiero et al.). Enhanced proliferation of Ly6C+ monocytes/macrophages, driven by CCL2/CCR2 signaling, contributes to chronic inflammation in diabetic wounds. While endogenous bone marrow progenitor cells are mobilized after wounding in diabetic mice, their homing to the wound site is limited. Targeting the CXCR4-CXCL12 axis can increase progenitor cell engraftment and stimulate angiogenesis and cell proliferation (Fiorina et al.). Impaired diabetic wound healing is also characterized by abnormal keratinocyte and fibroblast responses, abnormal macrophage polarization, impaired recruitment of mesenchymal stem cells and endothelial progenitor cells, and decreased vascularization. Prolonged expression of TNF-α in diabetic wounds further contributes to impaired healing (Xu et al.). In summary, diabetic wound healing is impaired by various factors, including abnormal cell migration, inflammation, and impaired progenitor cell recruitment, leading to delayed healing. Despite promising treatments like low-intensity laser irradiation and targeting the CXCR4-CXCL12 axis, challenges remain in overcoming chronic inflammation and cellular dysfunction.

Remodelling

Diabetic wound healing is a multifaceted process that faces significant challenges, particularly due to excessive inflammation, reduced angiogenesis, and altered extracellular matrix (ECM) deposition, which all contribute to delayed recovery (Dasari et al.). One of the crucial players in this process is microRNAs, which regulate various stages of wound healing, including inflammation, angiogenesis, and remodeling (Ozdemir and Feinberg). Iron, essential for normal bodily functions, also plays a role in wound repair. However, in diabetic wounds, there is an accumulation of iron in the late-stage repair phase, which promotes ECM deposition and remodeling, but at the same time, reduced iron levels and dysregulated iron gene expression are observed, with STEAP3 emerging as a key mediator in this process (Wilkinson et al.). Additionally, resolvins, which are pro-resolving mediators, target the resolution phase of wound healing by stimulating innate immune responses, enhancing microbial clearance, and resolving inflammation. They have shown to reduce neutrophil infiltration, increase macrophage phagocytic activity, and even improve insulin sensitivity, which makes them promising therapeutic agents for enhancing diabetic wound healing (Shofler et al.). The healing of diabetic wounds is hindered by chronic inflammation, impaired angiogenesis, and ECM deposition, with key molecular players like microRNAs, iron regulation, and resolvins offering insights into potential therapeutic avenues. Despite these findings, challenges remain in effectively translating these mechanisms into long-term, practical treatments.

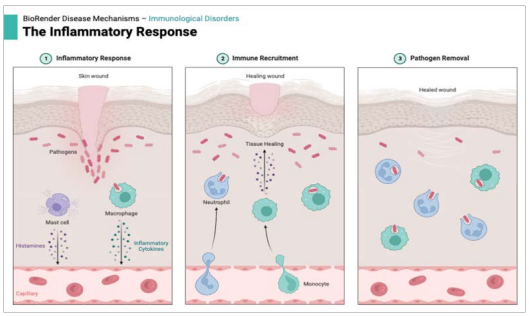

Figure 2 The Inflammatory Response is Initiated in Three Steps. Created with Penk, D. (2020) BioRender

Types of Diabetic Wounds

Diabetic Foot Ulcers (DFUs)

Neuropathic Ulcers

These occur in feet with nerve damage, leading to a warm and well-perfused foot with palpable pulses. The primary distinction between neuropathic

and neuro ischemic ulcers is the presence or absence of ischaemia. Ischaemia can be confirmed through the ankle-brachial pressure index (ABPI), where a value of less than 1 indicates ischaemia (Edmonds and Foster). Neuropathic ulcers show better healing outcomes compared to ischemic and neuro ischemic types, with a median healing time of approximately 75 days (Singh et al.). This results from inadequate blood supply, presenting as cool, pulseless feet, having a higher rate of non-healing and amputation (Singh et al.; Edmonds and Foster). Additionally, honey-based treatments have proven effective, with manuka honey-impregnated dressings significantly reducing healing time and promoting rapid disinfection of neuropathic diabetic foot ulcers compared to conventional dressings. These natural approaches offer alternative therapies for diabetic wound healing, addressing the challenges posed by compromised immune systems, neuropathy, and poor circulation in diabetic patients (Chauhan et al.). Diabetic wounds encompass a variety of types, primarily categorized based on their underlying pathophysiology. Understanding these classifications is crucial for effective management and treatment. The main types of diabetic wounds include diabetic foot ulcers (DFUs), which can be further divided into neuropathic, ischemic, and neuroischemic ulcers, as well as other wound types such as diabetic bullae and cellulitis (Figure 2).

Ischemic Ulcers

Diabetic foot disease has evolved over the past two decades, with an increase in ischemic/neuro-ischemic cases compared to purely neuropathic ones (Meloni et al.). Nerve decompression surgery has shown promise in reducing neuropathic diabetic foot ulcer recurrence risk and improving microcirculation (Nickerson and Yamasaki). The risk of non-healing is significantly higher in ischemic diabetic foot ulcers compared to neuropathic ulcers, and infected wounds at presentation are an important determinant of subsequent healing. Ischemic DFUs are associated with higher rates of non-healing and amputation (Singh et al.). Risk factors for ischemic heart disease in DFU patients include hypertension, male gender, smoking, and peripheral vascular disease (Waheed et al.). Impaired angiogenesis plays a crucial role in delayed DFU healing, prompting research into targeted angiogenic therapies (Canha and Soares). Early detection of neuropathy and timely foot care may help prevent ulceration and its consequences (Sadiq et al.).

Factors Affecting Diabetic Wound-Healing

Biochemical Disturbances

Elevated blood sugar levels in diabetes lead to biochemical changes that contribute to the formation of advanced glycation end-products (AGEs), which impair cellular functions and disrupt the normal wound-healing process. One of the primary consequences of these changes is the increased production of pro-inflammatory cytokines like TNF-α and IL-1β, which prolong the inflammatory phase and prevent proper healing progression (Berlanga-Acosta et al.; Swoboda and Held). Additionally, reducing tissue growth factors further exacerbates the imbalance, hindering healing (Wong et al.). However, recent research has shown that bone transport can induce the release of growth factors, offering potential therapeutic options to enhance healing in diabetic patients (Xie et al.). Further complicating this process, high glucose levels activate endothelial STING, a pathway that impairs angiogenesis, highlighting the crucial role of vascular factors in wound healing (Luo et al.). Another significant factor is the suppression of Wnt signaling, which has been identified as a contributor to impaired wound healing in diabetic foot ulcers (Sikri). Fibroblasts, which play an important role in wound healing, have also been identified as immunomodulatory factors in diabetic wound healing, indicating that their dysfunction contributes to the persistence of diabetic foot ulcers. Alarmingly, studies show that half of all patients with diabetic foot ulcers die within five years, underscoring the severity of the condition and the urgent need for effective treatment strategies (Liu et al.). In summary, these findings suggest that diabetic wound healing is impaired by a combination of elevated blood sugar, the formation of AGEs, increased pro-inflammatory cytokines, and a reduction in tissue growth factors. Vascular factors, Wntsignaling suppression, and fibroblast dysfunction further complicate the healing process. Emerging therapies such as bone transport

may offer hope for improving outcomes, but the high mortality rate among diabetic foot ulcer patients highlights the need for more effective and timely treatments.

Cellular Dysfunction

Diabetes has a profound impact on the body's ability to repair tissue, particularly by affecting the recruitment and differentiation of stem cells that are essential for wound healing. One critical process, re-epithelialization, is disrupted due to incomplete activation of keratinocytes, a major player in skin regeneration (Patel et al.). Additionally, mitochondrial dysfunction, common in diabetic wounds, worsens oxidative stress, inflammation and impairs angiogenesis, further delaying the healing process. However, recent research is uncovering innovative approaches to address these challenges. A promising solution is a poly(glycerol sebacate)-based hydrogel, which revitalizes mitochondrial metabolism, offering the potential for improving healing in diabetic wounds. Another exciting development is the use of a multifunctional hydrogel loaded with hypoxic mesenchymal stem cell-derived exosomes. These exosomes can regulate macrophage polarization, promoting a more favourable environment for healing (Shi et al.; Qi et al.). Stem cell-derived extracellular vesicles are also being explored for their potential to promote angiogenesis and recruit progenitor cells, key processes in wound healing. While cellular senescence, the process where cells lose their ability to divide, is often seen as detrimental, it has a dual role in wound healing. On the one hand, the senescence-associated secretory phenotype can contribute to tissue repair; on the other hand, when senescent cells accumulate abnormally, they can lead to excessive inflammation and tissue dysfunction. These findings provide new therapeutic targets for improving wound healing in diabetic patients, offering hope for more effective treatments (Kita et al.).

Vascular and Nutritional Factors

Diabetic wound healing is a complex process influenced by various factors, many of which stem from the systemic effects of diabetes. Vascular and nutritional deficiencies play a significant role in impairing the healing process. Studies have shown that diabetic foot patients often have low serum levels of critical nutrients such as albumin, hemoglobin, iron, and zinc, all of which are essential for effective wound healing (Lee et al.). These deficiencies contribute to the poor repair of tissues, highlighting the importance of maintaining proper nutrition in diabetic patients to promote healing. Beyond nutritional deficits, diabetes also affects various immune system components, including cellular responses, blood factors, and vascular tone, all of which further hinder the body's ability to heal wounds. Factors like oxygenation, infection, hormones, stress, obesity, medications, and lifestyle choices such as smoking and alcoholism all contribute to delays in wound recovery (Bhopale et al.). The pathophysiology of diabetic wound healing involves disruptions in immune and inflammatory functions, as well as atherosclerosis and angiopathy, which further complicate the healing process (Ahmed and Antonsen). One of the key challenges in diabetic wound healing is the vascular complications that reduce blood flow and impair oxygen delivery to the wounded tissue, exacerbating the delay in recovery. Microvascular dysfunction, which is often seen in diabetic patients, is not only linked to obesity-related organ damage but also plays a critical role in the development of cardiovascular risk factors such as hypertension and insulin resistance (De Boer et al.; Swoboda and Held). These factors interact to slow the healing process, and addressing them through nutritional management, better control of blood sugar, and improved vascular health may help improve wound healing outcomes in diabetic patients.

Reactive Oxygen Species

Reactive oxygen species (ROS) significantly impair diabetic wound healing, leading to oxidative stress and chronic inflammation. The crucial role of reactive oxygen species (ROS) in diabetic wound healing and explores novel nanomaterials for ROS scavenging, excessive ROS production in diabetic wounds leads to oxidative stress, impeding healing. While ROS are essential for normal wound healing processes, including angiogenesis and pathogen defense, excessive ROS production in diabetic

wounds leads to oxidative stress, impeding healing (Deng et al.). Bacterial biofilms contribute to chronic wound formation in diabetics, further complicating the healing process (Nouvong et al.). To address these challenges, antioxidant strategies have been explored to reduce oxidative stress-induced damage and improve wound healing outcomes (Deng et al.). One promising approach involves the activation of Nuclear factor erythroid 2-related factor 2 (Nrf2), which suppresses ROS activation and inflammation by releasing antioxidant proteins and inhibiting nuclear factor kappa B (NF-kB) dissociation (Ramachandran et al.). Programmed microalgae-gel treatments using Haematococcus have shown promise in providing antibacterial activity, oxygen supply, ROS scavenging, and immune regulation. Medicinal plants containing secondary metabolites like flavonoids and phenolic compounds have demonstrated anti-inflammatory, antimicrobial, and antioxidant effects in wound healing (Cedillo-Cortezano et al.). Understanding the complex interplay between ROS, bacterial biofilms, and antioxidant mechanisms in diabetic wound healing may lead to more effective therapeutic strategies for managing this challenging complication.

Microbial Infection

Diabetic wound infections present a significant challenge for patients, contributing to higher risks of amputation and a decreased quality of life (Rodríguez-Rodríguez et al.). The hyperglycemic environment in diabetic wounds creates an ideal setting for microbial infections, promoting the formation of biofilms that impair healing and make the tissue more susceptible to infection. Common bacterial culprits in diabetic wound infections include Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, with antibiotic-resistant strains becoming increasingly prevalent. Fungal pathogens, particularly Candida species, are also commonly found in these wounds (Nagpal et al.). Recent research has shifted focus towards understanding the relationship between the microbial communities colonizing diabetic wounds and the clinical outcomes of healing. This emerging area of study suggests that the composition of these microbial communities could serve as an important prognostic indicator, helping to predict the success of wound healing in diabetic patients (Wang et al.). By gaining a deeper understanding of the microbiological profiles of diabetic wounds, researchers are developing more effective treatment strategies. These may include modern wound dressings, advanced cell therapies, and bioengineered skin, which are designed to both promote healing and combat infections (Rozman et al.; Burgess et al.). One of the most troubling aspects of diabetic foot infections (DFIs) is the polymicrobial nature of these wounds, with studies revealing that 75% of DFIs are infected with multiple types of microorganisms, often dominated by Staphylococcus species. The presence of multidrug-resistant strains, such as methicillin-resistant Staphylococcus aureus (MRSA), further complicates treatment and management. New approaches to combat these infections are emerging, including oxygen-producing microneedle patches with antibacterial properties. These patches show promise in promoting wound healing by stimulating cellular processes while also fighting infections (Sun et al.). To better manage diabetic foot infections, researchers advocate for the development of refined antimicrobial guidelines that take into account regional variations in microbial patterns. Additionally, the judicious use of antibiotics is essential in addressing the growing issue of multidrug-resistant strains and ensuring that treatments remain effective (Jaber et al.; Makeri et al.). Diabetic wound infections are a major complication of diabetes, leading to an increased risk of amputation and reduced quality of life (Rodríguez-Rodríguez et al.). The hyperglycemic environment in diabetic wounds promotes biofilm formation, impairs healing, and increases susceptibility to infection. Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa are commonly isolated bacteria, with a high prevalence of antibiotic-resistant strains. Candida species are the predominant fungal pathogens (Nagpal et al.). Recent research has focused on the relationship between colonizing microbiota and clinical outcomes in diabetic wound healing, suggesting that microbial composition could serve as a prognostic indicator (Wang et al.). Understanding the microbiological profile of diabetic wounds is crucial for developing effective treatment strategies, which may include modern wound dressings, cell therapy, and bioengineered

skin (Rozman et al.; Burgess et al.). Diabetic foot infections (DFIs) present a significant challenge in diabetes care, characterized by complex microbial communities and impaired wound healing (Susan Silvia and Velrajan). Studies have revealed polymicrobial infections in 75% of DFI cases, with Staphylococcus species being predominant. The presence of multidrug-resistant strains, including methicillin-resistant Staphylococcus aureus (MRSA), complicates treatment. Innovative approaches, such as oxygen-producing microneedle patches with antibacterial properties, show promise in enhancing diabetic wound healing by promoting cellular processes and combating infections (Sun et al.). To improve DFI management, researchers recommend refined antimicrobial guidelines, considering regional variations in microbial patterns, and judicious use of antibiotics to address multidrug-resistant strains (Jaber et al.; Makeri et al.). Diabetic wound infections, often complicated by biofilm formation and antibiotic resistance, significantly impair healing and increase the risk of complications such as amputation. These studies emphasize the importance of understanding microbial composition as a prognostic tool for wound healing. Emerging treatments like micro-needle patches offer hope, and tailored antimicrobial guidelines are necessary to combat multi drug-resistant strains and improve patient outcomes.

Table 1 Effects of Medicinal Plants on Diabetic Wound Healing

S. No	Medicinal Plants	Active Constituents	Mode of Action	References
1.	Cassia auriculata	Quercetin, Kaempferol, Ellagic Acid, Catechins	Antioxidative effects by decreasing lipid peroxidation markers.	(Tietel et al.; Jeyashanthi and Ashok)
2.	Centella Asiatica	Asiaticoside, Madecassoside	Promotes angiogenesis, improves tensile strength.	(Rohmayanti and Hapsari; Liu et al.)
3.	Ocimum sanctum	Eugenol, camphor, α-pinene, alpha-carotene, verbenone	Promote wound closure in renal epithelial cells, and promote collagen density and fibroblast count in wound healing.	(Ezeorba et al.; Rery et al.)
4.	With ania somnifera	With a ferin A	Reducing inflammation and enhancing angiogenesis.	(Elsherbini et al.)
5.	Curcuma longa	Curcuminoids	Promotes diabetic foot ulcer healing by inhibiting miR-152-3p and activating the FBN1/TGF-β pathway, leading to reduced fibroblast apoptosis, and granulation tissue formation.	(Cao et al.; Panda et al.)
6.	Azadirachta indica	Nimbidin, azadirachtolide, 7-Deacetyl-7-oxogedunin	High binding affinity to insulin receptors in molecular simulations. Modulate cytokines, inhibit matrix metal loproteinases, and stimulate angiogenesis.	(Dhillon et al.; Abdullah et al.; Chanu et al.)
7.	Sanguisorba officinalis	flavonoids, and glycosides	Promote healing by suppressing inflammatory responses and modulating macrophage polarization through the NF-κB/NLRP3 pathway. Modulates MMP-mediated signaling pathways.	(Song et al.)
8.	Phyllanthus emblica	Ellagic acid, kaempferol, quercetin	Simvastatin improved wound healing in diabetic mice by enhancing angiogenesis and reducing neutrophil infiltration.	(Sultana et al.; Liao et al.)

9.	Allium sativum	Allicin, diallyl disulfide	Demonstrated significant antibacterial activity against wound infection pathogens, including MRSA.	(Tudu et al.)
10.	Sigesbeckia Orientalis	Sesquiterpene Lactones (Sigesbeckin)	Ameliorates diabetic nephropathy by reducing inflammation and oxidative stress. Regulates signaling pathways such as Wnt, Nrf2/ARE, MAPK, and PI3K/Akt to promote wound healing.	(Chen et al.; Zhou et al.)
11.	Lawsonia inermis	Lawsone (2-hydroxy-1, 4-naphthoquinone)	Accelerates wound healing by reducing inflammation, enhancing glucose uptake, and upregulating Igf-1 and Glut-1 expression. High bioactive content, promoting full re-epithelialization and well-organized collagen fibers.	(Daemi et al.; Rekik et al.; Purnima and Gadgoli)
12.	Calendula officinalis	Terpenoids, flavonoids, Careotinoids	Inhibits matrix metalloproteinases (MMPs) involved in chronic wound formation. Demonstrated its ability to accelerate the inflammation phase and increase granulation tissue production in acute wounds.	(Sapkota and Kunwar; Belal et al.; Givol et al.)
13.	Terminalia arjuna	Glycosides, flavonoids, tannins, and triterpenoids	Alleviates oxidative stress, promoting fibroblast activity, and reprogramming macrophage polarization. Manages hyperglycemia, stress-induced depression, and inflammation was comparable to established marketed drugs.	(Wu et al.; Tahsin et al.; Desai et al.; Kumar et al.)
14.	Tridax procumbens	Isorhamnetin, bixin, and lupeol	Accelerates wound healing by enhancing epithelial regeneration.	(Padmapriya et al.; Hogan et al.)

Emerging Therapies and Advanced Strategies in Diabetic Wound Management

Recent advancements in diabetic wound healing have seen a surge of innovative approaches that combine technology, natural compounds, and biological understanding to address the challenges faced by patients with diabetes. Among these, electrospun nanofiber dressings have shown great promise, with radially oriented PHBV patches loaded with berberine and sodium alginate/polyvinyl alcohol fibers containing Shikonin demonstrating significant potential in accelerating wound closure. These dressings offer sustained drug release, antimicrobial properties, and an ability to modulate inflammatory responses, vital for diabetic wound healing. Similarly, turmeric-derived nanoparticles incorporated into aerogels have proven effective in regulating multicellular networks and promoting healing. Epigenetic modifications have emerged as critical regulators in diabetic wound repair. These modifications, which influence inflammation, angiogenesis, and cell differentiation, involve mechanisms like histone modification and DNA methylation. Additionally, dual-functional scaffolds loaded with slow-release microspheres containing antibacterial agents and growth factors are being explored to both suppress bacterial growth and stimulate angiogenesis, accelerating wound healing (Hu et al.). A pH/glucose dual-responsive hydrogel has also been developed to scavenge reactive oxygen species (ROS) and release antibacterial drugs, further reducing inflammation and promoting wound closure (Hao et al.). The critical role of macrophage polarization in wound healing has been highlighted, with the transition from pro-inflammatory M1 to anti-inflammatory M2 macrophages being vital for effective repair. Dysregulation in this process can hinder recovery. Furthermore, studies have focused on various signaling pathways such as VEGF and TGF-β, with nanotechnology-based

approaches showing great promise in enhancing healing by targeting these pathways (Kamal et al.). However, key factors like prolonged inflammation, abnormal protease activity, and low oxygen levels continue to complicate the healing process. Natural compounds such as Piper crocatum Ruiz & Pav. have been found to promote wound healing through specific pathways in fibroblasts, while traditional Chinese medicine also provides promising insights into signaling pathways that aid in diabetic wound repair (Zhou et al.; Setyawati et al.). The gut-skin microbiota axis has also gained attention, with research suggesting that probiotics could influence the healing process through this connection (Patel et al.). Exosomes derived from epidermal stem cells have shown potential in enhancing diabetic wound healing (Zhou et al.). Innovative treatments such as exosome/metformin-loaded self-healing conductive hydrogels and endothelial progenitor cell (EPC)-targeted therapies are also being investigated. These approaches aim to repair microvascular dysfunction and promote wound healing by focusing on cellular regeneration and mitochondrial repair (Zhang et al.; Markandeywar et al.). Cold atmospheric pressure plasma is emerging as a therapeutic option with mechanical and biological benefits for diabetic wound care (Barjasteh et al.). Other novel approaches include oxygen-releasing antioxidant and antibacterial cryogel dressings like OxOBand, which have shown positive results in alleviating diabetic and infectious wound healing (Shiekh et al.). The focus on angiogenesis and vascular integrity is crucial for enhancing diabetic wound healing, with advanced bandages and self-healing hydrogels tailored to the specific needs of diabetic wounds (Matoori et al.; Qian et al.). Nanomaterials and nanotechnology also present multifunctional strategies to address diabetic wound healing (Bai et al.), with targeted therapies for oxidative stress showing promise in improving healing outcomes (Deng et al.). Bioactive scaffolds that promote M2 macrophage polarization are being engineered to accelerate angiogenesis and repair (Tu et al.), while sustained oxygenation systems are also helping to alleviate hypoxia and enhance epithelialization (Guan et al.). In summary, a variety of innovative therapies are emerging for diabetic wound healing, including advanced nanofiber dressings, epigenetic modulation, and novel hydrogels that target inflammation and promote angiogenesis. Natural compounds and traditional medicine are also being explored for their potential to regulate key signaling pathways. Key strategies focus on macrophage polarization, angiogenesis, and cellular regeneration, with nanotechnology, exosome therapies, and cutting-edge wound dressings offering promising solutions to the challenges of diabetic wound healing.

Conclusion

The literature data were obtained from online databases including PubMed, Springer, Scopus, BMC, WPR, Heliyon, and Research Gate using keywords such as “Diabetic wound healing”, “Phytotherapy”, “Herbal constituents”, “Growth Factors”, “Angiogenesis”, “Polyphenols”. Data extraction involved summarizing study designs, treatment types, mechanisms of action, efficacy and safety followed by a qualitative synthesis of findings. Furthermore, the scoping review included 35 studies, comprising preclinical trials, clinical trials, and observational studies, most studies examined the effectiveness of different plant-based therapies on the enhancement of diabetic wound healing, with common themes including improvement in the rate of wound closure, decreased inflammation, and increased collagen synthesis. Common results showed increased collagen synthesis, decreased inflammation, and improved wound closure rates. These results highlight the need for comprehensive studies aimed at improving plant-based treatments for diabetic wounds. Increasing funding for preclinical and clinical trials, encouraging cooperative research consortia, creating regulatory guidelines for the incorporation of phytotherapy into clinical practice, and assisting mechanistic studies to investigate molecular pathways are some specific suggestions for the advancement of this field. Initiatives supporting the sustainable production and harvesting of medicinal plants can also improve the affordability and accessibility of phytotherapy applications.

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Author Details

S. Raghavi, *Department of Biotechnology, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India,* ***Email ID****: raghavisel2006@gmail.com*

S. Haritha, *Assistant Professor, Department of Biotechnology, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India,* ***Email ID****: haritha2000rtn@gmail.com*

Mohamed Jameer Basha Jahankir, *Research Associate, Caldor Health Technologies Private Limited, Coimbatore, Tamil Nadu, India,* ***Email ID****: mohamedjameer2511@gmail.com*