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REVIEW

Insights into the mechanisms of diabetic wounds: pathophysiology, molecular targets, and treatment strategies through conventional and alternative therapies

Jagat Pal Yadav[1,2,3] · Ankit Kumar Singh[5] · Maria Grishina[6] · Prateek Pathak[7] · Amita Verma[3] · Vikas Kumar[4] · Pradeep Kumar[5] · Dinesh Kumar Patel[1]

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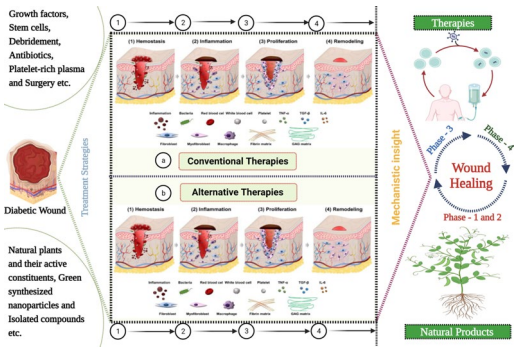
Abstract

Diabetes mellitus is a prevalent cause of mortality worldwide and can lead to several secondary issues, including DWs, which are caused by hyperglycemia, diabetic neuropathy, anemia, and ischemia. Roughly 15% of diabetic patient's experience complications related to DWs, with 25% at risk of lower limb amputations. A conventional management protocol is currently used for treating diabetic foot syndrome, which involves therapy using various substances, such as bFGF, pDGF, VEGF, EGF, IGF-I, TGF-β, skin substitutes, cytokine stimulators, cytokine inhibitors, MMPs inhibitors, gene and stem cell therapies, ECM, and angiogenesis stimulators. The protocol also includes wound cleaning, laser therapy, antibiotics, skin substitutes, HOTC therapy, and removing dead tissue. It has been observed that treatment with numerous plants and their active constituents, including *Globularia Arabica, Rhus coriaria* L., *Neolamarckia cadamba, Olea europaea, Salvia kronenburgii, Moringa oleifera, Syzygium aromaticum, Combretum molle,* and *Myrtus communis,* has been found to promote wound healing, reduce inflammation, stimulate angiogenesis, and cytokines production, increase growth factors production, promote keratinocyte production, and encourage fibroblast proliferation. These therapies may also reduce the need for amputations. However, there is still limited information on how to prevent and manage DWs, and further research is needed to fully understand the role of alternative treatments in managing complications of DWs. The conventional management protocol for treating diabetic foot syndrome can be expensive and may cause adverse side effects. Alternative therapies, such as medicinal plants and green synthesis of nano-formulations, may provide efficient and affordable treatments for DWs.

Graphical abstract



Keywords Stem cells · VEGF · FOXO1 · TGF-β1 · NF-kB · Diabetic wound

Abbreviations

AGEs	Advanced glycation end-products
ADSCs	Adipocyte-derived stem cells
CAT	Catalase
DWs	Diabetic wounds
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix

Extended author information available on the last page of the article

EGF	Epidermal growth factor
EMT	Epithelial–mesenchymal transition
EPCs	Endothelial progenitor cells
EST	Electrical stimulation therapy
FGF	Fibroblast growth factor
FTIR	Fourier transform infrared spectroscopy
FESEM	Field emission scanning electron microscopy
GSH	Glutathione
GPx	Glutathione peroxidase
GLUT-1	Glucose transporter-1
GNPs	Gold nanoparticles
HIF-1α	Hypoxia inducible factor-1α
HOTC	Hyperbaric oxygen therapy chamber
HVMPC	High-voltage monophasic pulsed current
IL	Interleukin
IRF	Interferon regulatory factor
IFN-γ	Interferon-γ
IGF-1	Insulin-like growth factor-1
JAK/STAT	Janus kinase/signal transducers and activators of transcription
LLLT	Low-level laser therapy
MAPK	Mitogen-activated protein kinase
miRNA	Micro-ribonucleic acid
MDA	Malondialdehyde
MMPs	Matrix metalloproteinase
NGF	Nerve growth factor
NPWT	Negative pressure wound therapy
NF-κB	Nuclear factor kappa B
PAD	Peripheral arterial disease
PLGA NP_S	Poly-lactic-co-glycolic acid nanoparticle
PBMT	Photo-bio-modulation therapy
pDGF	Platelet-derived growth factor
PGH2	Prostaglandin H2
PK-C	Protein kinase-C
ROS	Reactive oxygen species
SEM	Scanning electron microscope
SNPs	Silver nanoparticles
SOD	Superoxide dismutases
STZ	Streptozotocin
TNF-α	Tumor necrosis factor-α
TEM	Transmission electron microscopy
TGF	Transforming growth factor
T1DP	Type-1 diabetic patients
T2DP	Type-2 diabetic patients
TcPO2	Transcutaneous oxygen pressure
UPR	Unfolded protein response
UV–Vis	Ultraviolet–visible spectroscopy
VEGFR-2	Vascular endothelial growth factor receptor-2
WHO	World Health Organization
XRD	X-ray diffraction
ZnO NPs	Zinc oxide nanoparticles

Introduction

Diabetes is a complex metabolic disorder that affects a vast number of people worldwide, with more than 340 million individuals currently living with it. Unfortunately, over 20% of these individuals suffer from diabetes-related injuries, with the most common being leg or foot ulcers (World Health Organization 2014). The ability of people with diabetes to metabolize glucose is significantly impaired, and hyperglycemic conditions make the process of wound healing even more challenging. This often results in persistent and delayed injuries, which can have a significant impact on the quality of life. Unfortunately, the incidence of delayed healing in people with diabetes is increasing globally due to a lack of preventative and control measures.

This is a significant concern as approximately 2.5% to 15% of the global health budget is spent on diabetes mellitus annually, and diabetic wounds account for a significant proportion of this expenditure. According to a World Health Organization (WHO) study, diabetes could become the 7th leading cause of death by 2045. In 2014, around 9% of the global population suffered from diabetes, and this condition caused the death of 1.5 million patients in 2012 alone. Unfortunately, more than 80% of diabetes-related fatalities occur in low- and middle-income countries (World Health Organization 2013, 2014). One of the most significant risks of diabetes is the development of wounds in the legs and feet. These injuries can damage the skin, soft tissues, and even the bones, which can lead to an increased risk of infections in diabetic patients. In severe cases, amputations of the lower limbs may be necessary. Recent studies have revealed that around 60–80% of these wounds are capable of healing, but 10–15% of them may remain active, and 5–24% may ultimately result in leg amputations. It is crucial for diabetic patients to take measures to prevent such wounds from occurring, such as adopting a healthy lifestyle, monitoring blood glucose levels regularly, and seeking timely medical attention if any signs of injury or infection arise.

Proper care and management can minimize the risk of complications and improve the overall quality of life for people with diabetes (Vijayakumar et al. 2019; Talukdar et al. 2021; Yadav et al. 2022d). Diabetic wounds pose a significant health risk to individuals living with diabetes. In fact, more than 85% of all amputations in diabetic patients are preceded by ulceration that progresses to severe gangrene or infection. Shockingly, diabetic ulcers are estimated to affect around 6.4% of the world's population, with annual incidence rates ranging from 2 to 5% (Brocco et al. 2018; Adeleke et al. 2022; Ansari et al. 2022b). The prevalence of diabetic wound disease

is alarming, as it is estimated that between 19 and 34% of diabetes patients may suffer from this condition at some point in their lives. It is particularly prevalent in males, with 4.5% of men being affected, compared to 3.5% of women. Additionally, patients with type II diabetes (T2DP) are more likely to develop diabetic wounds, with 6.4% of cases compared to only 5.5% of cases in patients with type I diabetes (T1DP) (Talukdar et al. 2021).

Despite the high prevalence of diabetic wounds, epidemiological studies on this condition remain limited. This underscores the need for a more comprehensive and detailed understanding of the global impact of diabetic foot, which would be instrumental in devising effective prevention and treatment strategies. Improved healthcare practices and early intervention can minimize the financial burden on diabetic patients and promote better health outcomes (Zhang et al. 2017b; Yadav et al. 2022a). To accelerate the healing process of diabetic foot ulcerations, various interventions, such as control blood glucose level, wound debridement, off-loading pressure therapy, wound dressings, negative pressure wound therapy, hyperbaric oxygen therapy chamber, antibiotic therapy, platelet-rich plasma therapy, laser therapy, electrical stimulation therapy, growth factor therapy, stem cell therapy, bioengineered skin substitutes, and in extreme situations surgery, have been implemented (Alexiadou and Doupis 2012; Bekele and Chelkeba 2020).

In many countries, treating diabetic wound (DWs) through conventional methods is difficult due to its high cost, undesirable side effects, and shortage of vascular surgeons. This issue is particularly challenging in developing nations. As a result, there has been a growing interest in finding alternative remedies, such as medicinal plants, and their active constituents to help manage and prevent DWs complications (Ahmadian et al. 2021; Ansari et al. 2022a). Herbal remedies have been used for centuries to treat various ailments, including diabetes and diabetic wounds. With advances in modern research, we now have a better understanding of the pharmacological properties of phyto-compounds, the active compounds found in plants that can be effective for preventing and treating DWs conditions (Arumugam et al. 2013; Gaonkar and Hullatti 2020; Ansari et al. 2022a). Various plants including, *Globularia Arabica, Rhus coriaria* L., *Neolamarckia cadamba, Olea europaea, Salvia kronenburgii, Moringa oleifera, Syzygium aromaticum, Combretum molle, Myrtus communis, Terminalia chebula, Stryphnodendron adstringens, Euphorbia hirta* Linn., *Aloe Vera, Azadirachta indica, Teucrium polium, Gynura procumbens, Quercus infectoria, Pimpinella anisum, Punica granatum, Cycas thouarsii,* and *Ocimum sanctum,* have demonstrated potential for treating diabetic wounds by exhibiting anti-inflammatory, antimicrobial, antioxidant, and antibacterial, stimulating the blood coagulation and other anti-diabetic properties. These plants are relatively safe and have little-to-no side effects, suggesting that they may be effective treatments for diabetic wounds and speed up healing (Oguntibeju 2019; Sharma et al. 2021a; Vitale et al. 2022). Numerous natural compounds, such as quercetin, pongamol, neferine, plumbagin, luteolin, kirenol, kaempferol, arnebin-1, 20(S)-protopanaxadiol, myricetin, rutin, mangiferin, ginsenoside Rb1, berberine, and curcumin, have been isolated from plants and possess the potential to promote diabetic wound healing. These compounds can be utilized as an effective treatment throughout various stages of the wound-healing process, and there are numerous reports in the literature supporting their efficacy (Ansari et al. 2022b; Herman and Herman 2023). Clinical trials investigating the use of natural products in combination with modern drugs, as well as the development of improved delivery mechanisms, show great promise as a significant area for drug discovery from natural products. This represents an exciting avenue for the advancement of research in the field (Amirah et al. 2022).

The objective of this review article is to investigate the potential of traditional medicinal plants and their isolated phyto-compounds in the prevention and management of diabetic foot syndrome, as well as to analyze their future prospects as anti-diabetic medications.

Diabetic wounds (DWs)

DWs are a common type of skin injury that occurs in individuals with diabetes. Due to factors such as impaired blood flow and diabetic neuropathy, these wounds can be slow to heal and can lead to serious complications, such as infections and even amputation. Proper wound care, controlling blood sugar levels, off-loading, infection control, debridement, and wound closure are all essential components of treatment. Detecting and treating diabetic wounds early are vital to prevent further complications (Patel et al. 2019; Burgess et al. 2021). In DWs, persistent infections and microbial films are typical, and they are often associated with age, venous ulcers, high blood pressure, obesity, and diabetes (Avishai et al. 2017; Yadav et al. 2022c). The inflammatory phase in these wounds is disrupted, leading to an increase in neutrophils which release MMPs, creating an overabundance of reactive oxygen species (ROS), such as peroxide anion, hydroxyl ion, and superoxide anion (Sahakyan et al. 2022). This, in turn, leads to the destruction of ECM components, such as collagen, fibronectin, and vitronectin, along with an increase in inflammatory cytokines due to the excessive increase in pro-inflammatory macrophages, further maintaining the inflammatory phase (Zhao et al. 2016; Spampinato et al. 2020). Keratinocytes are hyperproliferative in diabetic wounds, but angiogenesis is compromised, and re-epithelialization is challenging. Managing these wounds requires a multi-faceted approach that addresses the various

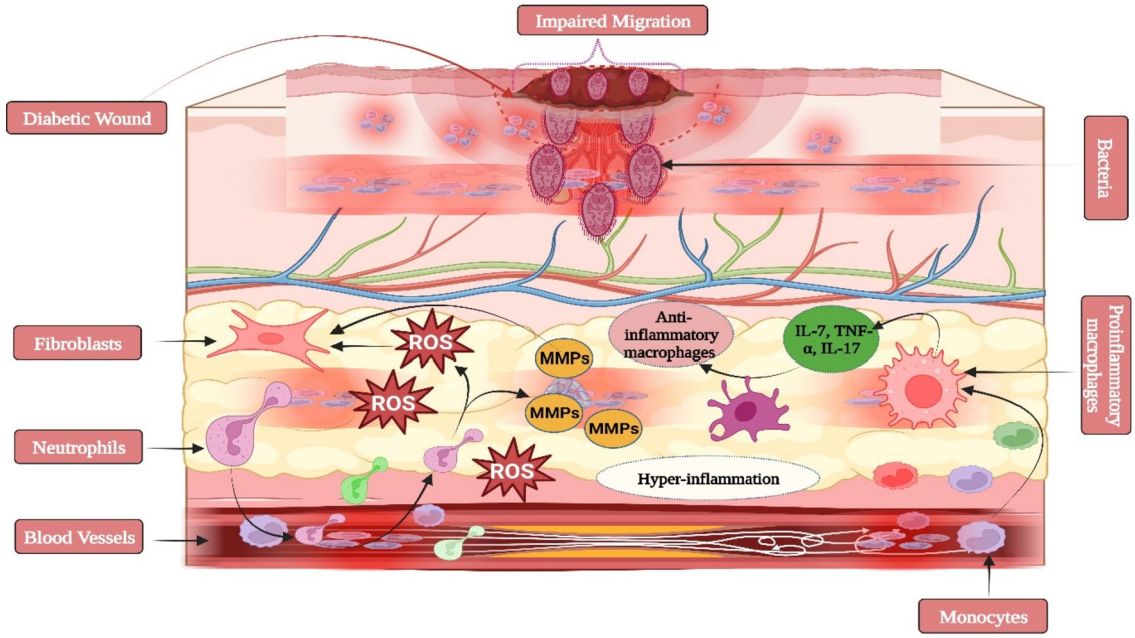


Fig. 1 In diabetic wounds, persistent inflammation and infections are common. Additionally, these wounds may exhibit hyperproliferative epidermis, fibroblast senescence, impaired migration, and elevated levels of matrix metalloproteinase. Abbreviations: IL-7, interlukin-7; IL-17, interlukin-17; MMPs, matrix metalloproteinase; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α

factors that contribute to their development and slow healing (Hosseini Mansoub 2022; Fang and Lan 2023). Illustration of the DWs is shown in Fig. 1.

Pathophysiology of diabetic wound

Diabetic wound healing requires harmonious interplay between biochemical mediators, inflammatory cells. This harmonious metastasis is triggered by various factors. The main contributors to this process are cellular macrophages derived from monocytes, which function as the primary sources of key pro-inflammatory cytokines. These cytokines, such IL-1β, IL-6, IGF-1, TGF-β, TNF-α, and VEGF, play pivotal roles in both normal wound healing and the distinct healing processes observed in diabetic condition (Veves et al. 2012). The detailed pathophysiology of DWs is explained through the schematic representation in Fig. 2.

DWs manifest as an intricate interplay of numerous factors, encompassing complications like diabetic neuropathy (DN), peripheral vascular disease (PVD), retinopathy, myopathy, and nephropathy. This intricate mechanism involves deficiencies in the angiogenic response, impaired functioning of neutrophils and macrophages, the generation of pro-inflammatory cytokines, and microvascular complications such as atherosclerosis. Additionally, compromised production of growth factors, hindered proliferation, and migration of fibroblasts and keratinocytes occur in diabetic wound-healing models. The cascade of events encompasses the blockade of nitrous oxide, inflammatory dysfunction of cells, hyperglycemia, hemoglobin glycation, impairment in cytokine production, dysfunction of MMPs, impaired collagen accumulation, down-regulation of neuropeptide expression, and an inflammatory response. Furthermore, there is a deficiency in the fibrinolysis inhibitor, pDGF modification, reduced epidermal nerve levels, and an imbalance between the ECM and MMPs (Yadav 2023).

Complications in diabetic wound

DWs are a significant contributor to diabetic wounds, often causing a delayed healing process that impacts patients' daily lives, morbidity, and mortality. These wounds can be categorized as delayed acute or chronic wounds, which compromise the healing process, resulting in impaired tissue generation. Diabetes also causes recurrent inflammation, hindering the development of mature granulation tissue and decreasing wound tensile strength, often attributed to ischemia-induced vascular disruption (Singh et al. 2023). It is essential to provide immediate treatment for all wounds, as they can be classified as either external or internal. External wounds, such as cuts, burns, bruises, and fractures, can go unnoticed in diabetic patients due to peripheral neuropathy. In contrast, internal wounds, such as ulcers and calluses, pose a high risk of bacterial infection, leading to tissue and

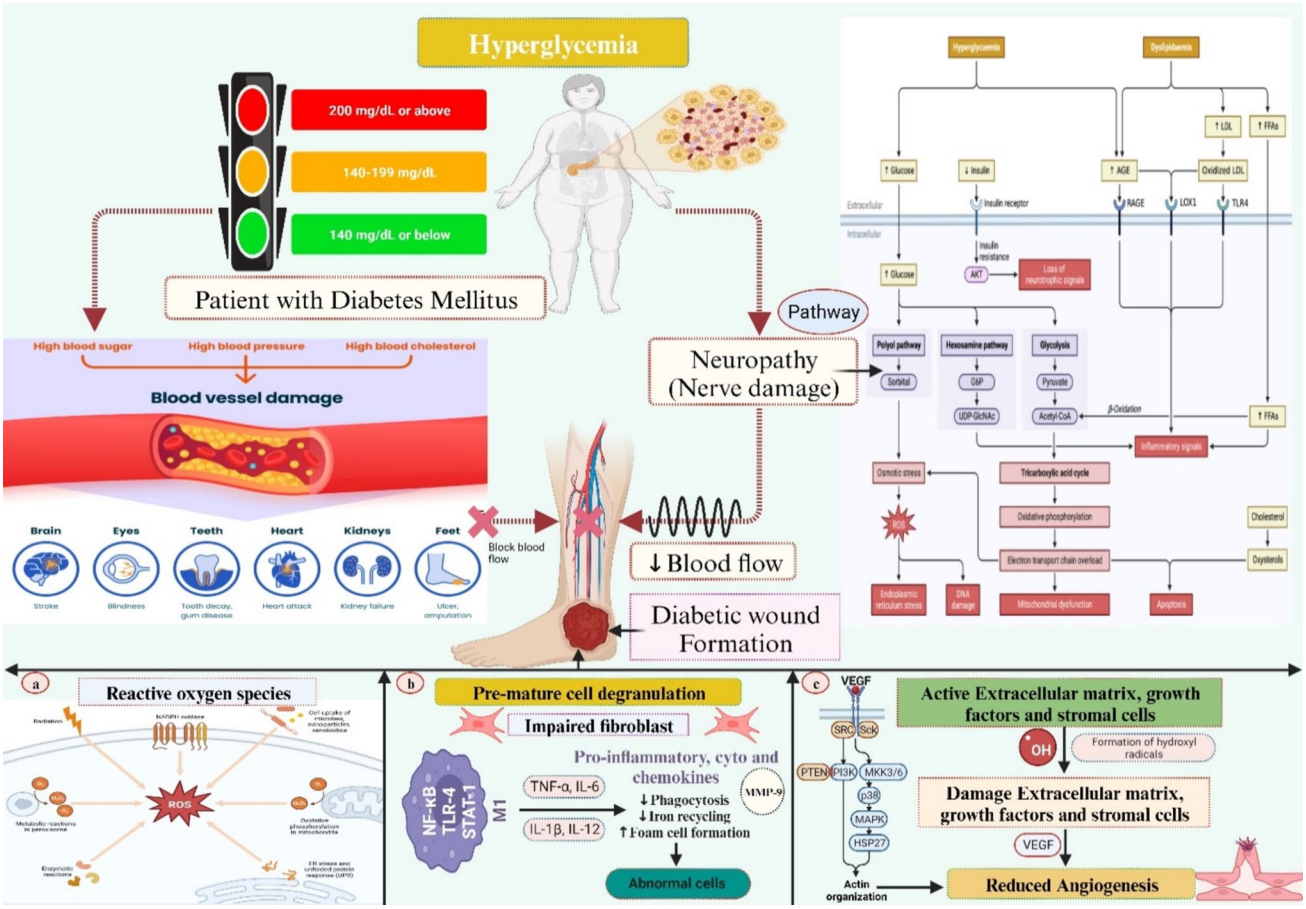


Fig. 2 Schematic representation of the pathophysiology of DWs. Abbreviations: AGE, advanced glycation end-products; FFAs, free fatty acids; IL, interleukin; LDL, low-density lipoprotein; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; MMP-9, matrix metalloproteinase-9; NF-kB, nuclear factor kappa-B; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; STAT-1, signal transducer and activator of transcription-1; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; UDP-GlcNAc, uridine diphosphate N-acetylgalactosamine; VEGF, vascular endothelial growth factor

skin damage (Petkovic et al. 2020; Fang and Lan 2023). Some of the factors responsible for DWs development are summarized in Fig. 3.

Diabetic wound mechanistic insight

Diabetes-related non-healing wounds can lead to a range of issues, including mental health concerns, such as anxiety and depression, functional limitations, difficulty with walking, and infection, which can manifest as cellulitis, abscesses, osteomyelitis, gangrene, and septicemia (Alsaimary 2010). While it is known that diabetic wound healing is impaired, the exact relationship between pathophysiology and wound healing in diabetes is still unclear. The healing process requires the cooperation of irritant cells and biochemical mediators. However, in diabetic patients, changes in cellular and metabolic processes and activities have been linked to the inability to heal wounds (Casqueiro et al. 2012).

Wound healing is a complex process that involves various cell types working together to repair the wound. These cells produce and regulate a range of cytokines and growth factors, including IL-1β, TNF-α, IL-6, VEGF, IGF-1, and TGF-β (Han et al. 2018). Monocytes, which eventually differentiate into macrophages, are responsible for the production of these factors in both diabetic and non-diabetic individuals. In addition to T-cells and B-cells, neutrophils also play a crucial role in producing TNF-α and IL-10. Other cell types, such as keratinocytes, fibroblasts, and mast cells, are also involved in the wound-healing process. The synthesis of VEGF, IGF-1, and TGF-β by these cells is equally important for effective wound healing (Babaei et al. 2013). Macrophages play a crucial role in the wound-healing process. However, changes in blood glucose levels and oxidative stress can cause alterations in the epigenetic coding, leading to changes in macrophage polarization and their control over this process. Dysregulated macrophage polarization is a primary cause of delayed wound healing (Maruyama

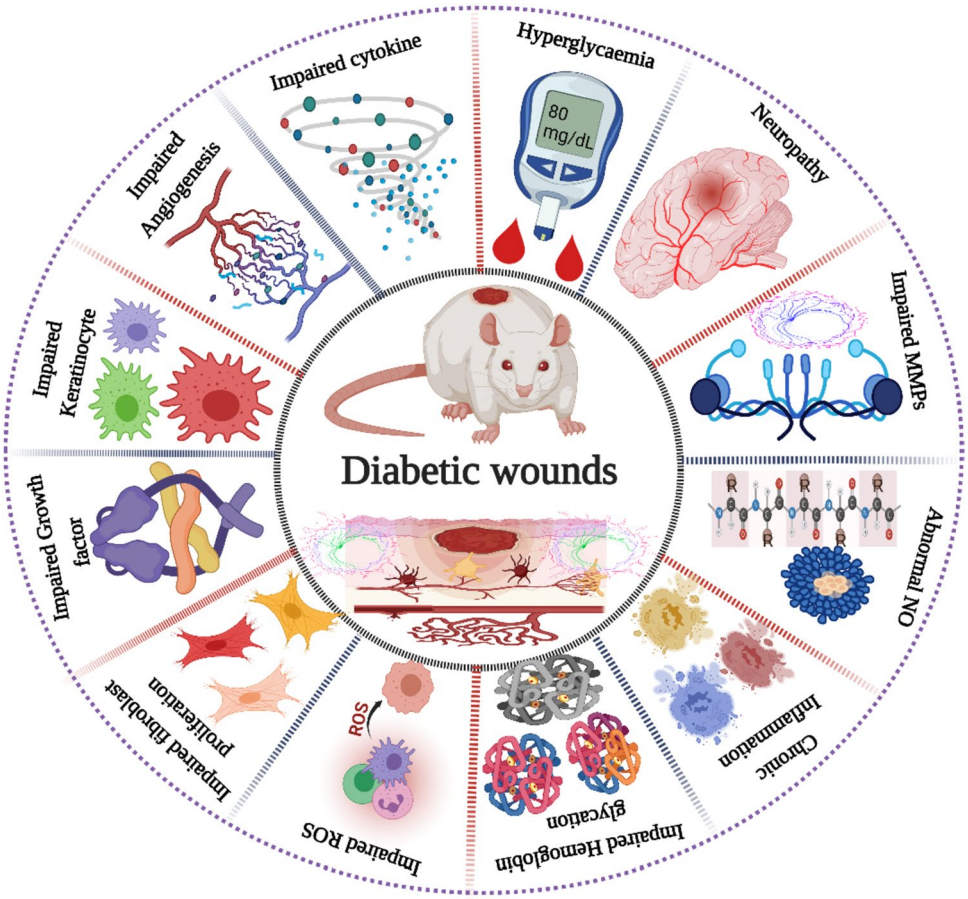


Fig. 3 Factors responsible for diabetic wound

et al. 2007; Basu Mallik et al. 2018). In diabetic individuals, wound healing is delayed due to complex chemical processes at the cellular level. Diabetic animal models have shown disruptions in healing-related factors such as growth factor production (Alavi et al. 2014). Activities, such as sustained production of pro-inflammatory cytokines, reduced angiogenic response, and microvascular complications, have also been reported in diabetic animal models (Loots et al. 2002). When it comes to the healing of diabetic wounds, a range of factors can impede the process. These include metabolic abnormalities, altered physiological responses, such as hypoxia resulting from glycation of hemoglobin and changes to red blood cell membranes, and the constriction of vascular passages (Brem and Tomic-canic 2007). Hypoxia occurs due to restricted blood flow, leading to a reduction in oxygen supply to the wound site. Hemoglobin glycation also reduces the availability of oxygen and nutrients to the affected tissue, leading to longer healing times (Avishai et al. 2017). The accumulation of unfolded proteins in the endoplasmic reticulum (ER) triggers a stress response in cells, known as unfolded protein response-8 (UPR8). This activation of unfolded protein response (UPR) is associated with the generation of pro-inflammatory mediators after tissue or skin damage. In diabetic wounds, the activation of UPR is prolonged compared to normal wounds, leading to increased production of pro-inflammatory chemokines (Schürmann et al. 2014). A summary of diabetic wound-healing mechanistic insights is illustrated in Fig. 4.

Microvascular problems in diabetes can significantly slow down the process of wound healing. miRNAs, which are noncoding RNAs of 19–24 nucleotides, play a crucial role in a wide range of physiological activities. Altered levels of miRNAs have been linked to disturbed wound healing and a variety of illnesses (Moura et al. 2014). Hence, one of the miRNAs, MiR-210, is elevated in hypoxia and targets E2f3, which inhibits keratinocyte proliferation during wound healing (Biswas et al. 2010). Another miRNA, MiR-200b, targets globin transcription factor-2 (GTF-2) and vascular endothelial growth factor receptor-2 (VEGFR-2), inhibiting angiogenesis. There are several types of miRNAs like miR-21, miR-130a, miR146a, miR-198, and miR-26 involved in diabetic wounds that regulate various processes, such as epithelialization, keratinocyte migration, fibroblast migration, re-epithelialization, and angiogenesis (Bhattacharya et al. 2015; Icli et al. 2016).

Diabetic patients often experience slow healing of wounds, and there are various factors that contribute to this phenomenon. Physiological factors, such as increased

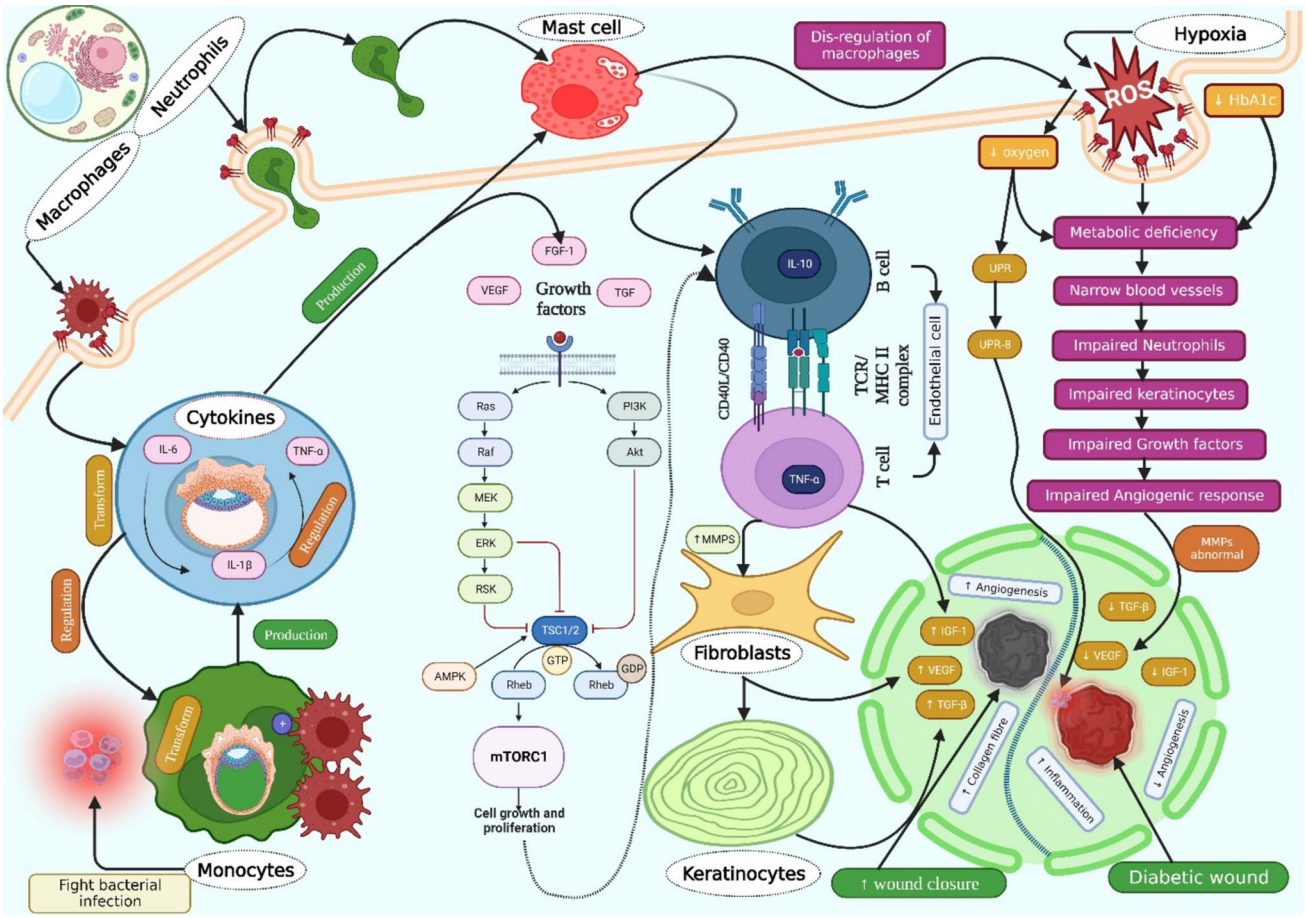


Fig. 4 Diagrammatical schematic representation of diabetic wound healing mechanistic insights. Abbreviations: AMPK, adenosine monophosphate activated protein kinase; AKT, protein kinase B; ERK, extracellular signal-regulated kinase; FGF-1, fibroblast growth factor; GTP, guanosine triphosphate; GDP, guanosine diphosphate; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; IL-1β, interleukin-1β; mTORC1, mammalian target of rapamycin complex 1; MMPs, matrix metalloproteinase; MEK, mitogen-activated protein kinase; Ras, rat sarcoma virus; Raf, rapidly accelerated fibrosarcoma; RSK, ribosomal S6 kinase, ROS, reactive oxygen species; PI3K, phosphatidylinositol 3 kinase; Rheb, ras homolog enriched in brain; TNF-α, tumor necrosis factor-α; TGF, transforming growth factor; TGF-β, transforming growth factor-β; UPR, unfolded protein response; VEGF, vascular endothelial growth factor

levels of serum MMP-9, impaired collagen accumulation, variation in collagen types, dysregulated neuropeptide expression in the skin, suppressed inflammatory response, deficiency of thrombin-activatable fibrinolysis inhibitor (Verkleij et al. 2010), and AGE11 modification of pDGF (Nass et al. 2010), are some of the factors responsible for delayed wound healing (Pradhan et al. 2011; Li et al. 2013). Furthermore, diabetic patients may also have decreased epidermal nerves, impaired epidermal barrier function, and an imbalance between the accumulation of ECM components and their remodeling by matrix metalloproteinase, which can also contribute to slow wound healing (Nass et al. 2010; Gooyit et al. 2014).

Treatment strategies for diabetic wound

Conventional therapies for DWs' complications

DWs are a common and challenging complication of diabetes mellitus, affecting an estimated 25% of patients with diabetes during their lifetime. These wounds often have poor healing rates, leading to prolonged hospital stays, increased healthcare costs, and decreased quality of life for patients. The treatment of diabetic wounds is complex and often requires a multi-faceted approach. In this study, we will review the current treatment strategies for diabetic

Table 1 Conventional treatment therapies used for the treatment of DWs

S. no	Therapies	Examples	Description	Benefits	Drawbacks	Citation
1	Control blood glucose level	Metformin and insulin therapy	Medication, diet, and exercise to maintain good control of blood sugar levels to promote wound healing	Reduces risk of infection and promotes diabetic wound healing	May require significant lifestyle change	Vatankhah et al. (2017)
2	Wound debridement	Surgical debridement, mechanical debridement and enzymatic debridement	Surgical, mechanical, or enzymatic removal of dead or infected tissue from the diabetic wound	Promotes healing and reduces risk of infection	May be painful and may require anesthesia	Haycocks and Chadwick (2012), Elraiyah et al. (2016), Dayya et al. (2022)
3	Off-loading pressure	Custom orthotics, specialized footwear, wheelchair or crutches	Specialized footwear, custom orthotics, or a wheelchair/crutches to reduce pressure on the diabetic wound site	Reduces pressure on the wound site and promotes diabetic wound healing	May be expensive and may require lifestyle changes	Bus (2016), Ahluwalia et al. (2021)
4	Wound dressings	Hydrogel, Hydrocolloid dressings and alginate dressings	Appropriate wound dressings to keep the wound moist, prevent infection, and promote healing	Can be tailored to the specific wound type and stage	May require frequent changes and monitoring	Güiza-Argüello et al. (2022)
5	Negative pressure wound therapy (NPWT)	Vacuum-assisted closure therapy	Application of suction to the wound to promote healing and remove excess fluid	Promotes wound healing and reduces swelling	May be expensive and require specialized equipment	Liu et al. (2017), Wynn and Freeman (2019)
6	Hyperbaric oxygen therapy chamber (HOTC)	Oxygen therapy chamber	Breathing pure oxygen in a pressurized chamber to increase oxygen delivery to the wound site and promote healing	Increases oxygen delivery to the wound site and promotes healing	May be expensive and require specialized equipment	Chen et al. (2017), Sharma et al. (2021b)
7	Antibiotics	Nafcillin, ceftazidime, cefazolin, clindamycin, dalbavancin, sulfamethoxazole and trimethoprim	Prescription of antibiotics to treat or prevent infections in the wound diabetic wounds	Can be effective in treating or preventing infections	Overuse can lead to antibiotic resistance	Lipsky et al. (2016), Ramirez-Acuña et al. (2019)
8	Platelet-rich plasma therapy (P-RP)	platelet-rich plasma and platelet-rich plasma gels	Injection and gels of platelet-rich plasma into the wound to promote healing	Stimulates tissue growth and reduces inflammation	Can be expensive and may require multiple sessions	Ahmed et al. (2017), Hirase et al. (2018)
9	Laser therapy	Low-level laser therapy and photobiomodulation therapy	Application of focused light energy to the wound to promote healing	Stimulates tissue growth and reduces inflammation	Can be expensive and may require multiple sessions	Kaviani et al. (2011), Moreira et al. (2021), Oyebode et al. (2021)
10	Electrical stimulation therapy	Electrical Stimulation	Application of electrical current to the wound to promote diabetic wound healing	Stimulates tissue growth and reduces inflammation and diabetic wound	Can be uncomfortable or painful for the patient	Abedin-Do et al. (2021), Melotto et al. (2022), Zheng et al. (2022)
11	Stem cell therapy	Mesenchymal stem cells and adipose-derived stem cells	Injection of stem cells into the wound to promote tissue regeneration and healing	Can stimulate tissue growth and reduce inflammation	Can be expensive and may require multiple sessions	Li et al. (2018), Lin et al. (2022), Ouyang et al. (2022)

Table 1 (continued)

S. no	Therapies	Examples	Description	Benefits	Drawbacks	Citation
12	Bioengineered skin substitutes	Apligraf and Dermagraft	Application of a synthetic or biologically derived skin substitute to promote wound healing	Can help to promote healing and prevent infection	Can be expensive and may require specialized equipment	Steinberg et al. (2010), Santema et al. (2016), Ren et al. (2022)
13	Nutritional supplements	Proteins, vitamin, and amino acids	Oral or parenteral administration of nutritional supplements to promote wound healing	Can help to support overall health and promote healing	May not be appropriate for all patients, and can cause adverse effects if taken in excess	Basiri et al. (2020), Bechara et al. (2022), Da Porto et al. (2022)
14	Surgery	–	Diabetic wound surgery is a surgical procedure performed to remove infected or necrotic tissue in diabetic patients with non-healing wounds, in order to promote healing and prevent further complications	Improved wound healing, reduced risk of infection, and prevention of further complications	Infection risk, wound recurrence, complications, high cost, and lengthy recovery time	Grande et al. (2020), Dasari et al. (2021)
15	Growth factors	Recombinant human platelet-derived growth factor, fibroblast growth factors, epidermal growth factor and vascular endothelial growth factor	Injection of growth factors into the wound to promote tissue regeneration and healing	Can stimulate tissue growth and reduce inflammation	Can be expensive and may require multiple sessions	Zubair and Ahmad (2019), Augustine et al. (2021), Zhou et al. (2021a)

wound complications, based on the available literature. It is important to note that the specific treatment plan for diabetic wound complications may vary depending on the individual patient's condition and the severity of the wound. A healthcare professional will typically assess the wound and develop a personalized treatment plan based on the patient's needs. Table 1 summarizes an overview of the conventional therapies for diabetic wound healing, including their description, benefits, and drawbacks.

Control blood glucose levels

Control of blood sugar levels is the cornerstone of DWs management. Elevated blood sugar levels can impair wound healing by decreasing collagen synthesis, impairing angiogenesis, and promoting oxidative stress. Medication, diet, and exercise are all essential components of blood sugar control in DWs care (Wang et al. 2023). Metformin, and other oral hypoglycemic drugs are commonly used medications for diabetes, which have been shown to improve wound healing by reducing inflammation and promoting angiogenesis. Insulin therapy is also commonly used to manage hyperglycemia in diabetic patients with wounds. Diet and exercise modifications can help control blood sugar levels and improve wound healing (Liu et al. 2022). A balanced diet rich in protein, vitamins, and minerals is essential for wound healing. Exercise has been shown to improve circulation and promote wound healing in patients with diabetes.

Metformin therapy Metformin is a medication commonly used to treat type 2 diabetes. While its primary use is to help control blood sugar levels, some studies suggest that it may also have benefits for wound healing in people with diabetes. Metformin has been shown to have anti-inflammatory properties and may improve blood flow to damaged tissues, which could potentially aid the healing process (Shi et al. 2022a). Some studies have also suggested that metformin may have antibacterial, anti-inflammatory, and diabetic wound-healing properties, which could help prevent infections in wounds.

Han et al. (2017) investigated wound healing, angiogenesis, and the number of circulating endothelial precursor cells (EPCs) in *db/db* mice, and the impact of metformin treatment on these parameters. Metformin therapy in these mice led to faster wound healing, improved angiogenesis, and increased circulating EPCs. The in-vitro experiments revealed that metformin treatment improved the function of bone marrow-derived EPCs (BM-EPCs) isolated from db/db mice, as shown by enhanced tube formation and NO production, and decreased levels of O_2^- Furthermore, metformin therapy significantly decreased the expression of TSP-1 in cultured BM-EPCs. These results suggest that metformin treatment may promote wound healing and angiogenesis in T2DM by stimulating NO production and inhibiting O_2^- and TSP-1 expression and inflammation in EPCs isolated from *db/db* mice (Han et al. 2017). In an another study, Cam et al. (2021) evaluated the efficacy of incorporating pioglitazone, metformin, and glibenclamide into chitosan/gelatin/polycaprolactone and polyvinyl pyrrolidone/PCL composite nanofibrous scaffolds for diabetic wound healing. The combination therapy resulted in the formation of hair follicles and improved regeneration of the dermis and epidermis in type-1 diabetic rats, while also reduced inflammatory cell infiltration and edema compared to single drug-loaded scaffolds. Furthermore, the combination therapy increased scaffold wettability and hydrophilicity, sustained drug release, and demonstrated high tensile strength and cyto-compatibility (Cam et al. 2021). Furthermore, Du et al. (2023) suggested that metformin (MTF) can work in coordination with mesenchymal cells (MSCs) to promote angiogenesis and wound healing in diabetic patients. The researchers found that MTF treatment activated the Akt/mTOR signaling pathway in MSCs, which in turn led to increased production of VEGF. VEGF is a key factor in promoting the growth of new blood vessels, which is essential for proper diabetic wound healing (Du et al. 2023).

Insulin therapy Insulin has been found to accelerate wound healing by controlling oxidative and inflammatory reactions. In rats with burn wounds, insulin therapy has been shown to decrease the levels of reactive oxygen species that can cause harm to lipids, proteins, and deoxyribonucleic acid (DNA) (Dhall et al. 2015). Additionally, insulin treatment has been observed to raise the levels of M2 macrophages and interleukin-10, leading to an anti-inflammatory effect that facilitates the removal of necrotic tissue from the wound (Chen et al. 2012). In addition, Vatankhah et al. (2017) investigated whether different diabetic treatment regimens have an impact on the healing of DWs. The researchers followed 107 diabetic foot ulcers in 85 patients until the wounds had healed, amputation was required, or a non-healing wound developed. The study found that insulin therapy significantly increased the wound-healing rate compared to other diabetic treatment regimens. After adjusting for multiple confounding co-variates, they also found that systemic insulin treatment can improve wound healing in DWs. The authors concluded that insulin therapy should be considered as a part of diabetic management for patients with DWs (Vatankhah et al. 2017). Furthermore, Yang et al. (2020a, b) demonstrated that the insulin-containing dressing could promote re-epithelialization, angiogenesis, and the deposition of extracellular matrix, specifically collagen, leading to accelerate wound healing. The researchers also found that HIF-1α, an important regulator of wound healing, was stable and accumulated in

wound cells treated with the insulin-containing dressing, but was significantly unstable in the control group. Furthermore, the study showed that insulin could counteract the destabilization of HIF-1α caused by methylglyoxal (MGO), a major form of AGEs in the diabetic state. Insulin facilitated the expression of HIF-1α target genes, promoting angiogenesis and extracellular matrix deposition, which are critical to wound healing (Yang et al. 2020a).

Wound debridement

Wound debridement is another essential component of diabetic wound care. Debridement is the removal of dead or infected tissue from the wound to promote healing. Surgical, mechanical, and enzymatic debridement are all effective methods of wound debridement (Bellingeri et al. 2016). Surgical debridement is the most invasive and is typically reserved for wounds with a significant amount of necrotic tissue. Mechanical debridement involves the use of a dressing or irrigation to remove dead tissue. Enzymatic debridement involves the application of topical enzymes to the wound to break down necrotic tissue (Haycocks and Chadwick 2012; Lázaro-Martínez et al. 2020) A retrospective study of patients with DWs treated for biofilm-associated infections found that sharp debridement combined with meshed skin grafts and negative pressure wound therapy (NPWT) resulted in a mean wound-healing time of 3.5 ± 1.8 weeks (Namgoong et al. 2020). Further analysis of debridement modalities found that surgical debridement was associated with shorter healing time, but there is a lack of strong evidence to support its efficacy in promoting wound healing (Elraiyah et al. 2016). However, various studies in both porcine and human models have shown that enzymatic debridement is another effective form of debridement that may reduce wound size, decrease inflammation, and increase granulation tissue. However, a secondary dressing may be required to penetrate the deeper layers of the wound to effectively control the biofilms present (Davis et al. 2017). Moreover, hydro-active dressings soaked with polyhexamethylene biguanide have shown promising results in promoting macrophage activation in the wound, inhibiting bacterial proliferation, and reducing inflammation in human studies (Mancini et al. 2017; Johani et al. 2018; Bain et al. 2020). In summary, while sharp debridement combined with meshed skin grafts and NPWT is effective in promoting wound healing in patients with DWs, other forms of debridement such as enzymatic debridement may also be effective. The use of hydro-active dressings soaked with polyhexamethylene biguanide is also a promising approach to promote wound healing and reduce inflammation.

Off-loading pressure therapy

Off-loading pressure therapy is also an essential component of DWs care. DWs often occur on the feet and can be exacerbated by pressure from walking or standing. While casting and non-removable walkers have traditionally been the go-to options for reducing plantar pressures in patients with diabetes, "diabetes footwear" has emerged as a promising alternative (van Netten et al. 2018). This type of footwear, including shoes and insoles designed to alleviate stress on the foot, has been shown to effectively reduce plantar pressures in a recent review and meta-analysis. The study highlighted the importance of features, such as metatarsal additions, apertures, and arch profiles for optimal results (Collings et al. 2021). Aside from footwear modifications, surgical off-loading is a viable option for patients suffering from diabetic foot ulcers (Ahluwalia et al. 2021). Achilles tendon release and foot reconstruction are two examples of surgical procedures that aim to optimize the foot for long-term off-loading. Studies have suggested that surgical off-loading may result in significantly better healing and amputation rates compared to non-surgical treatments. However, specialized footwear, custom orthotics, or a wheelchair/crutches can all be used to reduce pressure on the wound site and promote healing (Yammine and Assi 2022).

Wound dressings

The treatment and care of DWs present a significant global challenge due to their high amputation, recurrence, and mortality rates. Wound dressings have become a crucial aspect of DWs treatment, and continuous innovation has led to the development of advanced wound dressings with remarkable properties (Wang et al. 2021a). Among these, hydrogel, alginate, hydrocolloid, and foam dressings have gained popularity due to their exceptional moisture retention, biocompatibility, and therapeutic capabilities. In recent years, the pathogenesis of DWs has been better understood, leading to the development of functionalized dressings that have shown promising results in treating DWs. These advancements have brought significant benefits to the management and improvement of DWs (Ribeiro et al. 2009; Wang et al. 2021a).

Hydrogel dressings The unique potential of hydrogels for effective DWs dressing development lies in their remarkable ability to retain oxygen, absorb wound exudate, and maintain the moist environment that supports normal physiological processes in the wound bed (Kumar et al. 2017a). Moreover, hydrogels have shown promising results as antimicrobial substrates that help avoid tissue death and accelerate regular wound repair, and their porous structure promotes adequate exchange of gases, allowing the wound to breathe throughout wound healing and closure (Güiza-Argüello et al. 2022).

For instance, Lei et al. (2017) evaluated the ability of collagen hydrogels to promote angiogenesis and wound healing in diabetic rat models. Toward this, full-thickness wounds were induced and externally treated with a collagen hydrogel loaded with recombinant human epidermal growth factors. After 14 days of treatment, the rats treated with the fabricated hydrogel showed significantly smaller wound areas, indicating accelerated injury regeneration, relative to the group that did not receive a hydrogel treatment. Regarding angiogenesis, the proposed hydrogel dressing supported endogenous collagen synthesis, as well as the formation of vascularized scar tissue (Lei et al. 2017). In addition, Nilforoushzadeh et al. found that the use of pre-vascularized collagen/fibrin hydrogels on DWs patients resulted in increased hypodermis thickness and an accelerated wound-healing process (Nilforoushzadeh et al. 2020).

Alginate hydrogel dressings Alginate is a substance that has been extensively studied for its potential applications in tissue repair. One of its key properties is its ability to facilitate the attachment and activation of platelets and erythrocytes, which are crucial for wound healing. Alginate has been used to immobilize cells, enzymes, and peptides, and as a supporting matrix for drug delivery systems. Another advantage of alginate is that it is hydrophilic, which means that it can provide a moist environment that supports wound re-epithelialization and reduces the risk of bacterial infection (Sharmeen et al. 2019). Tellechea et al. (2015) investigated the use of alginate hydrogels to encapsulate anti-inflammatory substances: Substance P and Neurotensin, as well as human umbilical cord-derived outgrowth endothelial cells. The study used a mouse model of diabetes and found that the alginate hydrogels allowed continuous release of neuropeptides over a period of 10 days. This led to a significant reduction in wound size by approximately 80%. Furthermore, the addition of VEGF to the hydrogel improved and accelerated wound healing, resulting in a 40% decrease in wound size just after 4 days of treatment. These findings indicated a synergistic effect of the combination therapy, which supported the formation of new blood vessels (neovascularization) and promoted wound healing (Tellechea et al. 2015).

Hydrocolloid dressings Hydrocolloid dressings are occlusive dressings usually composed of a hydrocolloid matrix bonded onto a vapor-permeable film or foam backing. When in contact with the wound surface, this matrix forms a gel to provide a moist environment. Takeuchi et al. (2020) investigated the efficacy of hydrocolloid dressings combined with hydrogel in treating wounds in diabetic mice. The study revealed that the hydrogel treatment facilitated the formation of new blood vessels (angiogenesis) at the wound site. Moreover, the treatment boosted the proportion of macrophages with M2 polarization, which are known to support tissue repair and healing. As a result, there was an increase in the proliferation of fibroblasts, which are essential for wound healing. The study concluded that the use of hydrocolloid dressings with hydrogel can be an effective approach to promote the healing of non-infected DWs, even in the presence of high blood sugar levels (Takeuchi et al. 2020).

Negative pressure wound therapy (NPWT)

NPWT is a treatment approach used in the management of wounds, whether acute or chronic, for both short- and long-term care. NPWT involves the use of a specialized dressing that applies negative pressure to the wound bed, which can facilitate the removal of excess fluid, reduce inflammation and swelling, and promote the development of granulation tissue. These factors can lead to an acceleration of the healing process (Ji et al. 2021). In addition, Liu et al. (2017) performed a meta-analysis of randomized controlled trials to assess the effectiveness, safety, and cost-effectiveness of NPWT in treating lower leg ulcers caused by vascular issues, such as DWs. The results showed that NPWT had a positive impact on healing time and was well tolerated by patients, suggesting it as a promising therapeutic option for DWs (Liu et al. 2017). In an analysis of 11 trials, it was observed that NPWT was more effective than standard dressings in promoting complete ulcer healing, accelerating wound healing, and reducing wound surface area, without a substantial increase in adverse events. Similarly, Wynn and Freeman's (2019), extensive review found that NPWT was superior to standard treatment for treating DWs (Wynn and Freeman 2019). NPWT is typically continued as part of standard medical practice. It is important to note that NPWT may have additional benefits beyond promoting wound healing. Patients treated with NPWT showed earlier achievement of discharge criteria and the formation of granulation tissue, as well as significant reductions in leukocyte count, discomfort, and systemic inflammatory response (Gonzalez et al. 2017). There is ongoing debate about the impact of NPWT on tissue perfusion and oxygenation, as the results of various research methods have been inconsistent. While laser Doppler and thermal imaging have shown increased blood flow during NPWT (Wackenfors et al. 2005; Kairinos et al. 2013), transcutaneous partial oxygen pressure measurements have revealed a significant reduction in tissue oxygenation levels in DWs (Jung et al. 2016). However, this decrease in tissue oxygenation may actually be beneficial, as relative ischemia can stimulate neovascularization.

Hyperbaric oxygen therapy chamber (HOTC)

HOTC involves breathing pure oxygen in a pressurized chamber to increase oxygen delivery to the wound site and

promote healing. This therapy stimulates tissue growth and reduces the risk of infection, but it can be expensive and requires specialized equipment. According to recent studies, HOTC may have beneficial effects on patients with Wagner grade 3 and 4 ulcers, resulting in improved levels of HbA1c, leukocytes, and serum creatinine. However, it should be noted that there is a limited number of high-quality studies available on the use of HOTC for this purpose (Erdoğan et al. 2018). A meta-analysis conducted by Sharma et al. (2021a, b), has demonstrated a positive correlation between HOTC and improved rates of complete healing of DWs, as well as a reduction in the incidence of major amputations. However, the analysis did not show a significant decrease in the rates of minor amputations, overall amputations, or mortality, and the average ulcer percentage did not show improvement. Additionally, it was found that the HOTC group experienced more side effects compared to the group receiving conventional therapy. Thus, caution should be exercised when using HOTC in the treatment of DWs. Furthermore, there is an urgent need for well-designed, adequately sized, multicenter studies using rigorous methodology to assess the efficacy and safety of HOTC as an adjunctive therapy for DWs (Sharma et al. 2021b). A small-scale study consisting of 17 patients revealed that HOTC led to an increase in levels of VEGF, IL-6, insulin-like growth factor binding protein-3, fibrosis, angiogenesis, and adiponectin, while decreasing IFN-γ levels. Additionally, the therapy caused the NF-κB to localize and resulted in translocation of HIF-1α into the cytoplasm (Burgess et al. 2021). Furthermore, studies have demonstrated that prolonged HOTC treatment reduces neutrophil recruitment and adhesion, enhances oxygen dispersion to damaged tissues, diminishes inflammation, and modulates the healing process in patients with DWs (Chen et al. 2017; Baiula et al. 2020).

Antibiotics

Antibiotic treatment is often utilized as an adjunctive therapy in the management of DWs healing. Diabetic patients are particularly susceptible to bacterial infections, which can delay the healing process and increase the risk of complications. Antibiotics can help to eradicate bacteria and reduce the risk of infection, allowing the wound to heal more effectively (Perez-Favila et al. 2019). However, the use of antibiotics should be carefully considered and prescribed judiciously, taking into account factors, such as the type and severity of the infection, the patient's medical history, and potential side effects or adverse reactions. Additionally, the overuse or misuse of antibiotics can lead to the development of antibiotic resistance, emphasizing the importance of proper antibiotic stewardship in the treatment of DWs (Ramirez-Acuña et al. 2019). Although there is a dearth of prospective comparative studies, various antibiotics have shown efficacy in treating diabetic foot infections. Nafcillin, flucloxacillin, and dicloxacillin, as well as ceftazidime, cefazolin, and ceftriaxone, have been utilized with success. In addition, newer antibiotics, such as dalbavancin, oritavancin, and telavancin, have also demonstrated efficacy in treating diabetic foot infections (Singh and Gupta 2017). Nevertheless, it is important to exercise caution when prescribing antibiotics, taking into account factors, such as drug efficacy, safety, and potential for development of antibiotic resistance. Furthermore, future research efforts should aim to provide further insight into the optimal antibiotic treatment options for DWs (Lipsky et al. 2016).

Platelet-rich plasma therapy (P-RP)

For more than 3 decades, the use of autologous P-RP and platelet gel products have been found to accelerate the healing of DWs. This is attributed to the presence of numerous growth factors, such as PDGF, TGF-β1, and EGF, as well as antimicrobial actions, which are responsible for various positive outcomes, such as tissue regeneration, cell proliferation and differentiation, α-degranulation, and chemotaxis. These factors play a vital role in promoting wound healing by aiding in the repair and regeneration of damaged tissues, promoting the growth of new blood vessels, and reducing inflammation (Babaei et al. 2017; Hirase et al. 2018). Additionally, Mehrannia et al. (2014) reported a clinical case involving a 71-year-old man with type II diabetes who had severe foot injury due to his inability to sense hot surfaces. Despite receiving treatment at the hospital, the patient's condition did not improve. Consequently, P-RP therapy was chosen as a treatment option. The standard P-RP methodology (Bio-Act. Bio-Jel. Inc.) was employed to isolate the P-RP, which was then injected 4 mm into the wound. Within 20 d, signs of tissue regeneration were evident, and by the 8th week, the tissue had completely returned to its normal state (Mehrannia et al. 2014). In the study conducted by Ahmed et al. (2017), patients treated with P-RP gel demonstrated a significantly faster healing rate compared to the control group (68% vs. 86%). The use of P-RP gel resulted in accelerated recovery from DWs and a decreased risk of infection when compared to standard control treatments (Ahmed et al. 2017). Both topical and injectable P-RP treatments have demonstrated potential as a novel approach for treating DWs, with benefits that include accelerated healing and antimicrobial properties. However, additional research is necessary to determine the true efficacy of P-RP in the treatment of wounds. Further studies should focus on refining P-RP treatment protocols, identifying the optimal dosage and frequency of treatment, and investigating its long-term effectiveness and safety.

Laser therapy

Laser therapy has been used as a potential treatment option for DWs' healing. Diabetic wounds are a common complication of diabetes and can be slow to heal due to poor circulation, nerve damage, and other factors.

Low-level laser therapy (LLLT) LLLT, also known as cold laser therapy, has been shown to promote wound healing by increasing blood flow, reducing inflammation, and stimulating cell growth and repair. LLLT uses low-intensity lasers or light-emitting diodes to stimulate the cells in the affected area. Several studies have shown promising results for the use of LLLT in DWs' healing (de Sousa and Batista 2016). Kaviani et al. (2011) conducted a randomized, double-blind clinical trial involving 23 patients with DWs who received either placebo treatment ($n=10$) or LLLT in addition to conventional care ($n=13$) for at least 3 months. The LLLT used had a wavelength of 685 nm and an energy density of 10 J/cm^2. The results showed that LLLT reduced the healing time for DWs, as evidenced by a significant reduction in wound size compared to the placebo group after week four of treatment. After 20 weeks, eight patients in the LLLT group achieved full wound healing, while only three patients in the placebo group did so. Although there was no statistically significant difference between the LLLT and placebo groups, the LLLT group had a shorter mean time to full recovery 11 weeks, compared to the placebo group 14 weeks (Kaviani et al. 2011). In another study, conducted by Schindl et al. (1999) evaluated the number of treatments needed to achieve complete wound closure in 20 patients with ulcers of different underlying causes, including diabetes ($n=8$), vascular insufficiency ($n=5$), radio damage ($n=4$), and autoimmune vasculitis ($n=3$). The results of the study showed that radiation injury ulcers healed at a faster rate compared to diabetes-related ulcers. Additionally, wound healing was significantly slower in patients with autoimmune vasculitis compared to those with radiodermatitis. The study also revealed that wound size was a significant factor affecting healing time (Schindl et al. 1999). The promising outcomes reported in the current research on the use of LLLT for DWs highlighted the need for more comprehensive investigations in this domain. To obtain definitive evidence regarding the efficacy of LLLT as a treatment for DWs, there is a requirement for high-quality studies that are randomized, controlled, and double-blinded, with adequate designs and statistical significance. Furthermore, research is needed to gain a deeper understanding of the mechanism of action of LLLT in relation to DWs.

Photo-bio-modulation therapy (PBMT) The use of PBMT, utilizing red and near-infrared (NIR) wavelengths, is being examined as a promising therapy for enhancing the speed of DWs. PBMT regulates the expression of genes responsible for various cellular processes, such as cell division, migration, and differentiation, thereby promoting cell growth. Effective wound repair requires a coordinated process of cell proliferation, differentiation, and migration, all of which can be modulated by PBMT (Oyebode et al. 2021). Numerous experiments utilizing NIR lasers have been conducted Maiya et al., (2005) studied the impact of PBMT on DWs healing in alloxan-induced diabetic rats by applying PBMT at a visible wavelength (632.8 nm, He–Ne laser) with a fluence of 4.8 J/cm^2 for 5 d a week. According to the findings, wounds treated with lasers healed substantially more quickly and more effectively than those in the untreated control group (Maiya et al. 2005). In another study conducted by Houreld and Abrahamse (2007), the same wavelength (632.8 nm) was utilized, but the researchers applied significantly lower (5 J/cm^2) and higher (16 J/cm^2) fluences. The results of the study revealed that at a fluence of 5 J/cm^2, IL-6 expression, proliferation, and migration were all higher compared to those observed at 16 J/cm^2. While selecting the appropriate fluence and wavelengths may accelerate the healing process, it is crucial to carefully consider these factors when implementing PBMT (Houreld and Abrahamse 2007).

Electrical stimulation therapy (EST)

Diabetes can lead to the development of chronic wounds that are challenging to manage due to poor circulation and reduced sensation. In recent years, electrical EST has emerged as a non-invasive treatment option for DWs. By applying low-level electrical currents, EST can stimulate the healing process in these difficult-to-treat wounds. EST has been found to be effective in promoting wound healing by increasing blood flow to the affected area, promoting cell growth, fibroblast growth, and reducing inflammation. These benefits make EST a promising therapy for DWs healing (Melotto et al. 2022). In a recent study, Abedin-Do et al., (2021) investigated the impact of EST on diabetic human skin fibroblasts (DHSF) cells that play a crucial role in wound healing. The study examined how different intensities of direct current EST (100, 80, 40, and 20 mV/mm) affected the ability of DHSF to stick together and grow, as well as their production of cytokines and growth factors. Using various assays, the study found that EST at 20 and 40 mV/mm promoted the ability of DHSF to stick together, grow, and remain viable. Additionally, EST reduced the release of pro-inflammatory cytokines IL-6 and IL-8, while increasing the release of the growth factor FGF-7 in the 48 h following EST. The study also showed that the beneficial effects of ES on DHSF growth persisted for up to 5 days after the treatment (Abedin-Do et al. 2021). Recent, findings of a meta-analysis conducted by Zheng et al. (2022), suggest that EST

may offer therapeutic benefits for the treatment of diabetic foot ulcers. Despite the high degree of variability observed among the included studies, EST treatment was found to be effective in reducing ulcer size and promoting ulcer healing. Moreover, the meta-analysis identified pulsed current EST as having the potential to improve ulcer healing compared to direct current EST. However, to fully assess the safety and efficacy of EST in the treatment of DWs, further large-scale clinical trials are necessary (Zheng et al. 2022). Wang et al. (2021a, b) conducted a study to investigate the effects of high-voltage monophasic pulsed current (HVMPC) on the proliferation and migration of human umbilical vein endothelial cells (HUVECs). The study found that HVMPC stimulated the PI3K/Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways, leading to increased cell proliferation and migration. Overall, these findings suggested that the use of ES-chitosan dressing may offer promising therapeutic benefits for the treatment of diabetic wounds (Wang et al. 2021b).

Growth factors

The process of wound healing involves a harmonious interplay of various biological agents, such as growth factors, MMPs, cytokines, inflammatory cells, keratinocytes, fibroblasts, and endothelial cells. Growth factors, which are polypeptides with biological activity, play a pivotal role in all stages of the healing process (Barrientos et al. 2008; Zubair and Ahmad 2019). In the process of tissue development, the granulation phase is marked by the initiation of the early inflammatory phase, which is augmented by the activity of growth factors. However, growth factor deficiencies in compromised wounds can result from various factors, including inadequate expression, generation, release, or excessive degradation of these critical agents (Crovetti et al. 2004). The synthesis of ECM during the healing process requires a delicate balance between matrix production and degradation. This regulation is influenced by various factors, such as VEGF (Frank et al. 1995), IGF-I, IGF-II (Xie et al. 2013), TGF-β (Bitar and Labbad 1996), KGF (Werner et al. 1994), pDGF (Beer et al. 1997), EGF (Burstein 1987), and FGF (Hosokawa et al. 2000; Parkar et al. 2001). Interestingly, individuals with diabetes tend to exhibit significantly lower levels of both TNF-α and IL-6. Growth factors are crucial not only in initiating the wound-healing process, but also in sustaining it throughout its various stages. Autologous keratinocytes, fibroblasts, and stem cells have a crucial role in directly interacting with growth factors, such as pDGF, EGF, VEGF, FGF, and KGF, which are essential for healing diabetic wounds. Moreover, many agents can indirectly affect molecular targets, thereby influencing the expression of growth factors, cytokines, MMPs, NO, and angiogenesis-promoting factors. These indirect effects can have significant implications for biological processes, whether they are direct or indirect. Table 2 summarizes the various growth factors-based therapy for the treatment of diabetic wound.

Platelet-derived growth factor (pDGF) In DWs, the down-regulation of growth factor receptors and rapid degradation of growth factors contribute to the slowed healing process. One such critical growth factor is pDGF, a serum mitogen released by platelets, which plays a key role in stimulating fibroblast proliferation, matrix formation, and connective tissue maturation (Greenhalgh et al. 1990). During the late inflammatory phase, macrophages produce pDGF in the wound environment, attracting fibroblasts and inflammatory cells due to its cell proliferation stimulating properties. This, in turn, facilitates the synthesis of collagen, glycosaminoglycans, proteoglycans, and glycan's, ultimately leading to the production of granulation tissue proteins, provisional ECM, and angiogenesis (Doxey et al. 1995). The reduced expression of pDGF and its receptors in diabetic wounds further emphasizes the importance of this growth factor in the healing process. Several clinical trials have demonstrated the efficacy of pDGF in speeding up the wound-healing process (Lobmann et al. 2006; Li et al. 2008).

Basic fibroblast growth factor (bFGF) The bFGF plays a critical role in various biological processes, such as the development and differentiation of fibroblasts, proliferation of vascular smooth muscle cells and endothelial cells, metabolism of extracellular matrix, growth of mesodermal cells, and cell movements. It stimulates these cellular activities and facilitates the formation of granulation tissue, thereby accelerating the healing process. The increased pace and intensity of granulation tissue formation induced by bFGF contributes significantly to the wound-healing process (Tsuboi and Rifkin 1990).

Vascular endothelial growth factors VEGF is a potent angiogenic cytokine that is abundantly present in the skin, and its concentration in a wound plays a crucial role in the healing process. It supports the rate-limiting phases of vasculogenesis and angiogenesis by promoting the proteolytic degradation of the extracellular matrix of existing blood vessels and stimulating the migration and proliferation of capillary endothelial cells (Presta et al. 1997). In DWs, VEGF increases capillary density, enhances blood flow and metabolic rate, and promotes the formation of granulation tissue. Additionally, this protein regulates the re-vascularization and permeability of the wound site. VEGF receptor-1 and -2 activation can induce inflammation and angiogenesis, respectively (Angelo and Kurzrock 2007). However, diabetes can impair wound healing by reducing the local levels of VEGF. Studies have shown that aberrant VEGF receptor patterns, reduced VEGF mRNA levels, increased VEGFR-1

Table 2 Growth factor-based therapies used in diabetic wound healing reported in past 9 years (2015–2023)

S. no	Growth factor	Agonist	Administration of drug	Doses of drugs	Duration of therapy	Mode of action	Action/effect	Wound model	Diabetes induction	Citation
1	hEGF	Curcumin	Bandage	–	12 days	MSCs-EGF-Cur B	↑ diabetic wound closure; ↑ tissue formation; ↑ collagen deposition; ↑ angiogenesis; ↓ inflammation	Excision wound (Circular full thickness)	STZ	Mohanty and Pradhan (2020)
2	EGF	Hyaluronic acid, chitosan and insulin	Hydrogel	0.2 mg, 0.66 mL and 0.34 mL	12 days	ILM and EGF	↑ wound contraction; ↑ fibroblast; ↑ collagen and myofibrils; ↓ inflammation	Excision (Circular full thickness)	STZ	Zhu et al. (2020)
3	EGF	Silver and nanoparticle encapsulated growth factor co-loaded chitosan	Hydrogel	24-mM Ag + and 60-μgmL^{-1}	14 days	EGF	↑ wound closure; ↑ re-epithelialization; ↑ collagen deposition; ↑ collagen maturation	Excision (Circular full thickness)	STZ	Lee et al. (2021)
4	EGF	Poly (3-hydroxybutyrate-co-3-hydroxyvalerate)	Patch and hydrogel	100 ng, 150 μL and 100 ng/cm^2	30 days	EGF	↑ keratinocytes; ↑ fibroblasts, angiogenesis; ↑ endothelial cells; ↑ wound closure	Excision (Circular full thickness)	STZ	Augustine et al. (2021)
5	bFGF	Pelnac Gplus, Integra and Terudermis	Topical	51 μL and 10.16 μg/cm^2	21 days	bFGF	↑ wound healing; ↑ capillary formation; ↑ granulation tissue; ↑ re-epithelialization	Excision (Circular full thickness)	Diabetic mice	Notodihardjo et al. (2020)
6	EGF	Collagen hyaluronic acid scaffold	Topical	0.5, 1, 2 mg/mL	21 days	EGF, TGF-β, IL-6, VEGF, pDGF and SDF-1	↑ coagulation effect; ↑ chronic wound healing; ↑ neovascularization; ↑ Collagen deposition	Excision (Circular full thickness)	High fat diet and STZ	Wang et al. (2022)

Table 2 (continued)

S. no	Growth factor	Agonist	Administration of drug	Doses of drugs	Duration of therapy	Mode of action	Action/effect	Wound model	Diabetes induction	Citation
7	TGF-β3	Small Interfering RNA and Recombinant TGF-b Polypeptides	Injection	14 ng	10 days	TGF-β1, TGF- β2, and TGF-β3	↑ cornea wound healing; ↓ inflammation; ↑ re-epithelialization; ↑ gene expression	Excision (Circular full thickness)	STZ	Bettahi et al. (2014)
8	Fibroblast and Cytokines growth factor	Fibroblast Growth and the Secretion of Cytokines and Growth factors	Emulsion	100, 80, 40 and 20 mV/mm	10 days	IL-6 and IL-8	↑ cell adhesion; ↓ pro-inflammatory cytokines; ↑ growth factor (FGF-7); ↑ wound closure; ↑ re-epithelialization	Diabetic human skin fibroblast	Diabetic patient	Abedin-Do et al. (2021)
9	EGF, VEGF, TGF-β, pDGF	Midkine	Topical	10 ng/kg	28 days	MMP-8, pDGF, EGF and VEGF	↑ growth factor; ↑ wound closure; ↓ maintain oxidative stress; ↓ inflammation	Excision (Circular full thickness)	STZ	Dik Burak (2016)
10	rhFGF21	Heparin poloxamer	Hydrogel	2 and 10 µl,	17 days	rhFGF21	↑ diabetic wound closure; ↑ granulation tissue; ↑ re-epithelialization; ↑ expression of CD31	Excision (Circular full thickness)	STZ	Liu et al. (2019)
11	VEGF and TGF-β1	4-Hexylresorcinol	Ointment	2% 4HR	3 weeks	HIF, TGF-β1/ALK5/VEGF	↑ VEGF-A, and TGF-β1; ↑ angiogenic proteins; ↑ diabetic wound closure; ↑ capillary regeneration; ↑ epithelial thickness	Deep burn wound	STZ	Kim et al. (2020)

Table 2 (continued)

S. no	Growth factor	Agonist	Administration of drug	Doses of drugs	Duration of therapy	Mode of action	Action/effect	Wound model	Diabetes induction	Citation
12	Growth factors	Hyaluronic acid and growth factor	Topical and liposome	30 µL, 20 mg/mL and 100 µg/mL	17 days	EGF, IGF-I, pDGF-A	↑ fibroblast proliferation; ↑ procollagen; ↑ skin permeation; ↑ wound closure; ↑ re-epithelialization	Excision (Circular full	STZ	Choi et al. (2017)
13	rhEGF, EGF	rhEGF	Topical	2.06, 95% CI 0.35 to 12.22; I2 = 50%	84 days	rhEGF, EGF	↑ diabetic wound closure; ↑ cell migration; ↑ cell proliferation; ↑ angiogenesis	Diabetic foot ulcers	Diabetic patient	Yang et al. (2020b)
14	Keratinocyte growth factor	Elastin biopolymer	Hydrogel	2 µM, 2 + 500 nM	28 days	KGF, ELP	↑ keratinocyte proliferation and migration; ↑ angiogenesis; ↑ wound healing	Excision (Circular full thickness)	STZ	Devalliere et al. (2017)
15	Transforming growth factor-β1	TGF-β1	Osmotic pumps	1 mg/mouse/day	10 days	TGF-β1, VEGF, FGF	↑ angiogenesis; ↑ wound healing; ↑ granulation tissue; ↓ inflammatory markers	Excision (Circular full thickness)	STZ	Okizaki et al. (2015)
16	VEGF and TGF-β1	Deferoxamine	Ointment	0.1%	19 days	HIF-1α, SDF-1α, TGF-β1, TNF-α and MMP-9	↑ HIF-1α, VEGF, SDF-1α; ↑ TGF-β1, IL10 and mRNA; ↓ TNF-α, MMP-9 and IL-1β; ↑ cutaneous wound healing	Excision (Circular full thickness)	STZ	Ram et al. (2015)
17	EGF	Polyurethane and silk fibroin	Topical	8 mg/ml	21 days	MMP-9, IL-10	↑ collagenization; ↑ re-epithelialization; ↑ diabetic wound healing	Burn wound	STZ	Sen et al. (2020)

Table 2 (continued)

S. no	Growth factor	Agonist	Administration of drug	Doses of drugs	Duration of therapy	Mode of action	Action/effect	Wound model	Diabetes induction	Citation
18	Growth factor	Silver and calcium alginate nanoparticles	Topical	200 µL	15 days	EGF, VEGF	↑ diabetic wound closure; ↓ inflammation; ↑ Collagen deposition; ↑ Growth factor	Excision (Circular full thickness)	STZ	Choudhary et al. (2021)
19	VEGF	Bilirubin	Ointment	0.3, 5, and 90%	19 days	IL-1β and MMP-9	↑ HIF-1α, VEGF, SDF-1α, TGF-β1, and IL-10; ↑ mRNA and protein levels; ↓ IL-1β and MMP-9; ↑ Collagen deposition; ↑ diabetic wound closure	Excision (Circular full thickness)	STZ	Ram et al. (2016)
20	VEGF	PLGA and VEGF	Topical	0.9% w/v, 5 mg and 5 µg	21 days	VEGF and VEGFR2	↑ collagen content; ↑ re-epithelialization; ↑ angiogenesis; ↑diabetic wound healing; ↑ granulation tissue formation	Excision (Circular full thickness)	db/db mice	Chereddy et al. (2015)
21	VEGF	Shixiang Plaster	Topical	2 mm	14 days	NF-kB, RAGE, VCAM-1 and eNOS	↑ VEGF and CD34; ↑ granulation tissue; ↑ angiogenesis; ↑ diabetic wound closure	Excision (Circular full thickness)	STZ	Fei et al. (2019)
22	VEGF-C	Adipose-derived mesenchymal stem cells	intradermal	1%, 0.5 mM, 1 mM to 10 mM and 200 mM	14 days	EGFR3, METTL3 and METTL3/IGF2BP2-m6A	↑ proliferation, migration and lymph angiogenesis; ↑ diabetic wound healing; ↓ Inflammation	Excision (Circular full thickness)	STZ	Zhou et al. (2021a)

Table 2 (continued)

S. no	Growth factor	Agonist	Administration of drug	Doses of drugs	Duration of therapy	Mode of action	Action/effect	Wound model	Diabetes induction	Citation
23	bFGF	bFGF and ERK1/2	NPWT	125 mmHg	7 days	bFGF and ERK1/2	↑ bFGF and collagen; ↑ diabetic wound closure; ↓ inflammation; ↑ granulation tissue formation	Excision (Circular full thickness)	Diabetic patient	Yang et al. (2014)
24	VEGF	Extracorporeal shock wave	Topical	800 impulses at 10 kV	6 weeks	VEGF and MAPK	↑ diabetic wound healing; ↑ VEGF, eNOS, and Ki-67; ↓ inflammation; ↑ granulation tissue formation	Excision (Circular full thickness)	STZ	Chen et al. (2019)
25	S-bFGF, EGF	Hyaluronate and collagen	Topical	0.3, 1 and 2.5 μg/cm^2	7 days	S-EGF, S-bFGF	↑ S-EGF and S-bFGF loaded on HCD matrix; ↓ Inflammatory marker; ↑ diabetic wound healing	Excision (Circular full thickness)	STZ	Choi et al. (2016)
26	IGF	Insulin factor	Topical	1% and 3%	21 days	α-smooth muscle actin and IGF-1	↑ rapid re-epithelialization; ↓ inflammatory marker; ↑ expression of myofibroblasts; ↑ diabetic wound healing	Excision (Circular full thickness)	Alloxan	Achar et al. (2014)
27	EGF and aFGF	EGF and aFGF	Intravenous drip	40 IU/cm^2 and 40 AU/cm^2	60 days	EGF, FGF	↑ epidermal healing rate; ↑ granulation tissue growth; ↑ cell proliferation; ↓ inflammatory marker; ↑ diabetic wound closure	Burn wound	Diabetic patient	Xu et al. (2018)

Table 2 (continued)

S. no	Growth factor	Agonist	Administration of drug	Doses of drugs	Duration of therapy	Mode of action	Action/effect	Wound model	Diabetes induction	Citation
28	FGF	4-Morpholineethanesulfonic acid	Hydrogel	25 µL	14 days	FGF-2	↑ angiogenesis; ↓ inflammatory marker; ↑ granulated tissue; ↑ wound closure	Excision (Circular full thickness)	STZ	Xiong et al. (2022)
29	EGF	Carboxymethylcellulose	Hydrogel	2%	12 weeks	EGF, pDGF and FGF	↑ granulated tissue; ↑ wound closure; ↓ inflammatory marker; ↑ remodeling tissue; ↑ collagen deposition	Chronic wound, an ulcer size greater than 2 cm2	Diabetic patients	Pessanha et al. (2023)
30	VEGF-C	Lymphangiogenesis	F8–VEGF-C fusion protein target	200 and 500 µm	7 days	VEGF-C or VEGFR-3	↑ granulated tissue; ↑ wound closure; ↓ inflammatory marker; ↑ remodeling tissue; ↑ collagen deposition	Excision (Circular full thickness)	(db/db) mice	Brunner et al. (2023)
31	VEGF	20(S)-Protopanaxadiol of Ginseng	PPD or PBS	25 µM	8 days	VEGF-ERK	↑ granulated tissue; ↑ wound closure; ↓ inflammatory marker; ↑ remodeling tissue; ↑ collagen deposition	Incision (full thickness)	STZ	Park et al. (2023)

aFGF, acidic fibroblast growth factor; bFGF, basic fibroblast growth factor; EGF-Cur B, epidermal growth factor -curcumin bandage bioconjugate; EGF, epidermal growth factor; ELP, elastin-like peptides; EGFR3, epidermal growth factor receptor 3; ERK1/2, extracellular signal-regulated protein kinases; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; HIF-1α, hypoxia-inducible factor-1α; HIF, hypoxia-inducible factor; hEGF, human epidermal growth factor; ILM, internal limiting membrane; IL-6, interlukin-6; IL-8 interlukin-8; IGF, insulin-like growth factor; KGF, keratinocyte growth factor; MAPK, mitogen-activated protein kinase; MSCs, mesenchymal stem cells; MMP-8, matrix metalloproteinase-8; NF-kB, nuclear factor kappa B; PLGA, Poly (lactic-co-glycolic acid); pDGF, platelet-derived growth factor; RAGE, receptor for advanced glycation end-products; rhFGF21, recombinant human fibroblast growth factor 21; rhEGF, recombinant human epidermal growth factor; STZ, streptozotocin; SDF-1 stromal cell-derived factor-1; SDF-1α, stromal cell-derived factor-1α; TGF-β1, transforming growth factor-β1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule 1; VEGFR-2, vascular endothelial growth factor receptor-2

levels, and decreased VEGFR-2 levels are the primary reasons for non-healing wounds (Zhou et al. 2015).

Endothelial growth factors, Insulin-like growth factor, and transforming growth factor-β Activation of the EGF receptor by platelets leads to the secretion of EGF, which in turn stimulates epidermal cell growth, cellular motility, migration, mesenchymal regeneration, angiogenesis, and cell proliferation (Hardwicke et al. 2011). The insulin-like growth factor complex, comprising IGF-1 and IGF-2 peptides, is also involved in diabetic wound healing. IGF-1 plays a critical role in the granulation and re-epithelialization of cells, enhances the chemotaxis of endothelial cells, and promotes the proliferation of keratinocytes and fibroblasts, thereby facilitating wound repair. In contrast, diabetic individuals exhibit reduced expression of IGF-1, suggesting that an aberration in cell granulation may contribute to the pathogenesis of diabetes. Additionally, the pH of the wound environment significantly influences the binding affinities of these growth factors (Brown et al. 1997; Bruhn-Olszewska et al. 2012). Studies have shown that both diabetic animals and humans have lower levels of IGF-1 and TGF-β in their wound tissue, which is associated with delayed healing process (Bhora et al. 1995; Galiano et al. 2004). TGF-β plays a critical role in wound healing by promoting the recruitment of inflammatory cells, such as neutrophils, macrophages, lymphocytes, and keratinocytes, stimulating fibroblasts, and generating growth factors. These events accelerate vascularization, angiogenesis, and ECM synthesis while inhibiting ECM breakdown (Roberts 1995). Reduced TGF-β concentration is a potential reason for delayed healing in diabetes patients. Notably, several studies have demonstrated that TGF-β1-dependent inhibitory elements in the promoter region of MMP-encoding genes can reduce MMPs production, leading to excessive degradation of growth factors (Veves et al. 2012). Transcription factors, such as Smad-2, Smad-3, and Smad-4, can either activate or repress TGF-β target genes, including those encoding for MMPs and collagen (Hozzein et al. 2015). Decreased TGF-β1 levels enhance the activation of inflammatory cells, leading to a delay in the healing process in diabetic wounds. Diabetics are hypothesized to have lower levels of TGF-β1 and higher levels of TGF-β3, resulting in increased macrophage activity, higher production of reactive oxygen species, and prolonged inflammation (Jude et al. 2002; Heublein et al. 2015). In summary, decreased levels and expression of growth factors, such as TGF-β and IGF-1, contribute to the delayed wound healing observed in diabetes.

Stem cell therapy

Stem cell treatment has an advantage over growth factor therapy in DWs, because stem cells can govern tissue regeneration in a comprehensive manner by refining the microenvironment at the wound site. While neither therapy is perfect in repairing DWs, stem cell therapy has a higher success rate. Stem cells have been found to exert a beneficial influence on a range of pathophysiological processes, such as wound healing, by enhancing cellular activities required for tissue repair, augmenting the formation of extracellular matrix, and stimulating angiogenesis in ischemic tissue. Animal experiments have revealed that implantation of stem cells can improve circulation in previously ischemic extremities by creating a favorable wound site microclimate (El Hage et al. 2022).

Kirana et al. (2012) evaluated the efficacy, safety, and viability of bone marrow-derived cellular product transplantation in improving microcirculation and reducing amputation rates in diabetic subjects with critical limb ischemia and diabetic ulcers. The study included two groups: one receiving Bone Marrow Mesenchymal Stem Cells (BM-MSCs) and the other receiving expanded bone marrow cells enriched in $CD90^{+}$ tissue repair cells (TRCs). Patients were followed up for 52 weeks following treatment, and wound healing, ankle-brachial index and TcPO2, reactive hyperemia, and angiographic imaging were measured before and after cell therapy. The results showed that both treatments were safe and feasible, with subjects undergoing BM-MSCs treatment showing significantly improved outcomes in ulcer-healing rate and ankle–brachial index compared to TRCs. However, there was no significant difference in TcPO2. Microcirculation improved in some transplanted patients in both groups, but some patients experienced adverse events, such as subarachnoid bleeding and death due to multiple organ failure following sepsis (Kirana et al. 2012). In a mouse model of DWs, Kim et al. (2012) discovered that intradermal injections of human amniotic mesenchymal stem cells (MSCs) were more effective in promoting wound healing compared to human autologous adipose-derived stem cell (ADSCs) or human dermal fibroblasts (Kim et al. 2012). In addition, Ren et al. (2019a, b) demonstrated that utilizing adipose stem cell-derived microvesicles for wound treatment substantially increased the production of growth factors, such as VEGF, pDGF, EGF, and FGF2. This led to enhancements in epithelialization, angiogenesis, and collagen deposition, ultimately resulting in an accelerated wound-healing rate (Ren et al. 2019b). In another research study, Li et al (2018) conducted research demonstrating that adipose-derived stem cell-secreted exosomes reduced ulcer size in diabetic mice by promoting angiogenesis, granular tissue development, immunosuppression, and a reduction in oxidative stress-related proteins (Li et al. 2018).

ADSCs have emerged as a promising therapeutic avenue for tissue regeneration. Recently, Shi et al. (2022a, b) demonstrated that a circular RNA known as Snhg-11, secreted from ADSCs, could enhance DWs healing by potentially

inducing M2 macrophage polarization through modulation of the miR-144-3p/HIF-1α/STAT-3 signaling pathway (Shi et al. 2022b). In another study, Ouyang et al. (2022) demonstrated that overexpression of hematopoietic Prostaglandin-D synthase (HPGDS) in ADSCs accelerated the healing of DWs. HPGDS is a cytosolic protein that can convert prostaglandin H-2 (PGH-2) to prostaglandin-D-2 (PGD-2). The study found that HPGDS overexpression improved the anti-inflammatory state and promoted M2 macrophage polarization, contributing to faster wound healing (Ouyang et al. 2022).

Bioengineered skin substitutes

Managing DWs using the conventional therapy approaches can be problematic due to their poor healing potential. However, recent advancements in tissue engineering, bioengineered skin substitutes, and genetic growth factors have resulted in significant breakthroughs for addressing this challenge. These technological innovations have played a pivotal role in improving the treatment outcomes of DWs (Ren et al. 2022). Santema et al. (2016) conducted a systematic review to evaluate the effectiveness of skin substitutes in addition to standard care for treating DWs, using the Cochrane Collaboration's methodology. Seventeen randomized clinical trials comprising 1655 participants were included in the review, and the risk of bias varied across the studies. Thirteen studies compared standard care to skin substitutes and found that the use of skin substitutes in conjunction with standard care significantly increased the likelihood of full wound closure at 6–16 weeks compared to standard care alone [risk ratio 1.55, 95% (confidence interval) 1.30–1.85]. No significant differences in efficacy were found between different skin substitutes in the four studies that compared two different products. Two studies reported lower limb amputation rates, and when the results were combined, the rate was significantly lower in patients treated with skin substitutes (risk ratio 0.43, 95% CI 0.23–0.81), although the absolute risk difference was minor (− 0.06, 95% CI − 0.10 to − 0.01). Therefore, the review provides evidence that using skin substitutes in combination with standard care can enhance complete ulcer closure in diabetic foot ulcers (Santema et al. 2016). In an another meta-analysis, Gordon et al (2019) analyzed 25 studies that assessed wound closure rates after 12 weeks and found that biologic dressings were 1.67 times more effective than standard of care dressings in promoting healing of diabetic wounds, with a statistical significance of ($p < 0.00001$). Additionally, their analysis of 5 trials demonstrated that biologic dressings were 2.81 times more likely to result in complete wound closure at 6 weeks compared to standard of care (SOC) dressings, with a statistical significance of ($p = 0.0001$). The majority of the 31 studies, which evaluated the healing time of diabetic wounds, indicated that biologic dressings were more effective than SOC dressings, with 29 out of 31 studies recommended biologic dressings as the preferred treatment option (Gordon et al. 2019).

Nutritional supplements

The process of wound healing is intricate and necessitates adequate nutrients to repair damaged soft tissues. Unfortunately, malnutrition is a prevalent and often overlooked issue among patients suffering from diabetes and chronic wounds. Furthermore, there is currently a lack of clear guidance or reliable data regarding the use of nutritional supplements to enhance wound healing in individuals with DWs. Various nutritional supplements, such as proteins, vitamins, and amino acids, are discussed as potential adjuncts to promote the healing of DWs (Da Porto et al. 2022).

Protein and amino acid supplements Proteins and amino acids are commonly used as nutritional supplements to accelerate the healing of diabetic foot wounds, owing to their established effectiveness. Notably, there are randomized controlled trials (RCTs) specifically examining the impact of protein or amino acid combination supplementation on wound healing among individuals with DWs. Basiri et al. (2020) investigated the impact of combining a nutrient-dense formula with nutrition education on wound healing in patients with DWs. The study enrolled 29 patients who were randomly assigned to either the treatment group ($n = 15$) receiving nutritional supplements and education or the control group ($n = 14$) receiving only standard care. Wound healing was evaluated through planimetry at baseline and every 4 weeks for up to 12 weeks. No significant differences were observed between the groups at baseline for age, body mass index (BMI), duration of diabetes, wound age estimation, or wound area. The treatment group demonstrated a significantly faster wound-healing rate, with a 6.43 mm^2/week more reduction in wound area compared to the control group. The mean reduction in wound area during the first 4 weeks was almost 13 times greater in the treatment group (18.0 mm^2/week) compared to the control group (1.4 mm^2/week). The study findings suggested that combining nutrition supplementation with education can significantly accelerate wound healing in DWs patients compared to standard care alone (Basiri et al. 2020, 2022). In another study, Armstrong et al. (2014) conducted a randomized controlled trial with 270 patients, to investigate the impact of arginine, glutamine, and b-hydroxy-b-methyl butyrate supplementation on healing of DWs. No significant differences were observed between the groups in wound closure or healing duration after 16 weeks. However, subgroup analysis revealed that patients at risk of limb hypo-perfusion and/or hypoalbuminemia demonstrated accelerated healing of DWs, when these supplements were added to the stand-

ard treatment (Armstrong et al. 2014). Wong et al. (2014) found that after 2 weeks of supplementation with beta-hydroxy-beta-methylbutyrate (HMB), arginine (Arg), and glutamine (Gln), there was a statistically significant increase in the percentage of viable tissues ($p = 0.02$). Additionally, the experimental group showed a significant increase in pressure ulcer scale for healing (PUSH) scores within 1 week of supplementation ($p = 0.013$). Although wound size and PUSH scores did not appear to decrease with the administration of specialized amino acid supplements, tissue viability may have increased after 2 weeks (Wong et al. 2014).

Vitamin "C and D" supplement Vitamin C, also known as ascorbic acid, is a vital water-soluble nutrient that is essential for numerous tissue repair and maintenance functions, including collagen synthesis, immune system regulation, and the health of cartilage and bones. In addition, bone development requires two minerals, calcium and phosphorus, and the absorption of these minerals is facilitated by vitamin D, a fat-soluble vitamin with well-established benefits (Bechara et al. 2022).

Yarahmadi et al. (2021) found that the administration of vitamin E (200 IU/day) and vitamin C (250 IU/day) supplements for 8 weeks, along with platelet-rich plasma-fibrin glue dressing and negative pressure wound therapy device, significantly improved wound healing in patients with non-healing DWs (Yarahmadi et al. 2021). Kostadinova et al. (2019) reported that in recent RCTs with limited sample sizes, vitamin C supplementation may expedite the healing of DWs. One such trial conducted in Australia involved seven patients with DWs receiving (500 mg) of slow-release vitamin C capsules twice a day for 8 weeks, which resulted in a greater percentage reduction in ulcer volume compared to the placebo group in a randomized, placebo-controlled study (Gordon et al. 2019). Currently, only a few randomized controlled trials (most of which involve the same study group) have evaluated the effects of vitamin D supplementation on wound healing in DWs. However, a double-blind, placebo-controlled, RCTs conducted on 60 patients with grade 3 DWs based on "Wagner-Meggitt" criteria showed that after 12 weeks of intervention, vitamin D supplementation resulted in a significant reduction in ulcer length, width, depth, and erythema rate compared to the placebo (Razzaghi et al. 2017). According to Karonova et al. (2020), administering high-dose cholecalciferol therapy (40,000 IU/week) for a period of 24 weeks resulted in the normalization of 25(OH)D levels and led to improvements in neuropathy severity, skin microcirculation, and cytokine profile. Specifically, there was a reduction in pro-inflammatory IL-6 and an increase in anti-inflammatory IL-10. These findings suggested that vitamin D insufficiency may be a treatable factor that affects diabetic peripheral neuropathy, and highlighted the need for prompt identification and treatment with cholecalciferol at doses greater than 5000 IU/day (Karonova et al. 2020).

Surgery

Diabetic wound-healing surgery aims to promote healing of wounds in diabetic patients that are not healing properly on their own (Yang et al. 2016). The underlying theory is that diabetes can cause damage to blood vessels and nerves, leading to poor circulation and decreased sensation in the feet and legs. This can result in wounds that are slow to heal and prone to infection (Ji et al. 2022). Surgical intervention can help to address these issues and promote healing. Debridement (Yammine and Assi 2022), for example, can remove dead or infected tissue from the wound, allowing healthy tissue to grow and heal. Skin grafting can provide a new, healthy layer of skin to cover the wound and promote healing. NPWT can promote healing by removing excess fluid and increasing blood flow to the wound. HOTC can promote healing by increasing oxygen levels in the body, which is important for wound healing (Han and Ceilley 2017; Everett and Mathioudakis 2018). It is important to note that diabetic wound-healing surgery is typically only considered after non-surgical treatments have been tried and failed. Proper wound care, including keeping the wound clean and dry and changing dressings regularly, is also crucial for successful wound healing. Additionally, maintaining good blood sugar control is important in promoting healing and reducing the risk of complications (Kavitha 2014; Rezvani Ghomi et al. 2019).

Alternative therapies for DWs' complications

Natural plants and their active constituents-based treatment strategy in diabetic wound healing

Animal (pre-clinical) in-vitro and in-vivo based studies The delayed and impaired wound-healing process is a major issue in diabetic wounds (Kulprachakarn et al. 2017). Medicinal plants are a well-known source of therapeutic treatments, utilized in both conventional and alternative medicine (Ansari et al. 2022a). These traditional remedies possess several therapeutic properties, including wound-healing, antioxidant, antimicrobial, anti-inflammatory, and anti-hyperglycemic activities. Studies indicate that natural remedies are generally used for wound dressing, with few taken orally to treat DWs (Oguntibeju 2019). Traditional healthcare practices such as Ayurveda, Unani, traditional Chinese medicine, and other traditional health systems have significantly contributed to the healing of wounds in diabetic foot syndrome. In western nations, these medical systems are regarded as conventional and alternative medicine, as they incorporate medicinal herbs, acupuncture, dietary

therapy, massage, and therapeutic exercise for treating and preventing diseases (Li et al. 2011). Chinese herbal medicine, a primary component of traditional Chinese medicine, is widely used in clinical practice to treat DWs (Debnath et al. 2014; Wang et al. 2019). The healing process is accelerated by medicinal herbs due to their active constituents, which act in various ways. These include promoting the proliferation of fibroblasts, initiating the early expression of growth factors, exhibiting free radical scavenging or antioxidant activity, halting wound bleeding, preventing microbial growth, enhancing collagen synthesis and strength, increasing blood flow to wounds, reducing cellular damage, promoting DNA synthesis, facilitating wound contraction and epithelialization, and stimulating the production and migration of keratinocytes (Veves et al. 2012; Pis and Altunkaynak 2014).

Alsarayreh et al. (2022) demonstrated the wound-healing potential of a 10% plant extract from *G. arabica* in non-diabetic and diabetic rats. The healing process was notably associated with the utilization of a 10% plant extract, leading to a substantial improvement in wound contraction, as evidenced by statistically significant p values (< 0.025) in both non-diabetic and diabetic rats. This highlights the robust wound-healing capabilities of *G. arabica* extract. The treatment also demonstrated an increase in hydroxyproline and collagen expression, further emphasizing its effectiveness. In both non-diabetic and diabetic rat models, *G. arabica* extract exhibited significant wound-healing properties, as evidenced by enhanced wound contraction and elevated levels of hydroxyproline and collagen expression (p values < 0.025). This underscores the potent wound-healing capacity of the plant extract. Notably, during the initial phases of wound healing, *G. arabica* treatment upregulated IL-6 levels, contributing to the observed positive effects on wound contraction and hydroxyproline and collagen content. This suggests that the induction of cytokine production, such as IL-6, may play a role in expediting the wound-healing process. Furthermore, in this study explored the impact of *G. arabica* extract on a fibroblast cell line. Treatment with a 20 µg/ml methanolic extract resulted in a significant increase in cell migration (p values < 0.035), indicating substantial wound-healing activity. This finding further supports the notion that *G. arabica* extract promotes efficient wound healing, potentially through the stimulation of fibroblast migration (Alsarayreh et al. 2022). Moreover, Yadav et al. (2022a, b, c, d) reported the wound-healing potential of *Neolamarckia cadamba* extract in diabetic rats. Phytochemical analysis showed the presence of alkaloids, flavonoids, phenols, saponins, steroids, glycosides, and tannins in the extract. The extract caused significant wound contraction in both oral (28.70%, 36.80% at doses of 200, 400 mg/kg/day) and topical (23.08%, 31.21% at doses of 5%, 10% w/w/day) treated groups compared to the diabetic control. The oral treatment with the extract also decreased serum glucose levels and improved biochemical and enzymatic status in the body. Histopathological investigations demonstrated a dose-dependent improvement in wound healing by re-epithelialization, collagenation, and vascularization of damaged skin samples. These findings suggested that *Neolamarckia cadamba* extract may be effective in promoting wound healing in diabetic rats (Yadav et al. 2022b). In addition, Elnahas et al. (2021) evaluated the antimicrobial and wound-healing potential of Tanta LEM crude extract, obtained from olive leaves, against Methicillin-resistant *S. aureus* (MRSA). The extract showed significant antimicrobial activity against MRSA with an MIC value of 15.6 mg/ml. The checkerboard dilution technique demonstrated a synergistic interaction between Tanta LEM crude extract and Ciprofloxacin. The extract also exhibited high scavenging activity against 2,2-Diphenyl-1-picrylhydrazyl (DPPH) free radicals. In-vivo experiments on normal and diabetic rats treated with a combination of Shea butter and Tanta LEM extract showed the maximum wound contraction and healing activity. These findings suggested that Tanta LEM crude extract may be a promising agent for the treatment of MRSA infections and diabetic wound healing (Elnahas et al. 2021). Moreover, De Souza de Aguiar et al. (2021) investigated the wound-healing potential of alcoholic extract from *Stryphnodendron adstringens* (SAHE). Phytochemical analysis showed the presence of phenolic compounds, tannins, and flavonoids in the extract. SAHE showed strong antioxidant activities and induced fibroblast proliferation without being cytotoxic. The combination of SAHE and hydrogen peroxide showed a more pronounced healing activity than other treatments in both non-diabetic and diabetic animals, promoting angiogenesis and re-epithelialization. These findings suggest that SAHE may be a promising agent for promoting wound healing (De Souza de Aguiar et al. 2021). In a study, Hashemnia et al. (2019) examined the effect of *Pimpinella anisum* treatment on wound healing in 60 rats. The treated animals showed significantly reverted oxidative changes of total antioxidant capacity, malondialdehyde, and glutathione peroxidase induced by diabetic wounds ($p < 0.05$). Furthermore, it significantly increased the dry matter and hydroxyproline contents at various stages of wound healing ($p < 0.05$). Additionally, *Pimpinella anisum* treatment resulted in significant improvements in re-epithelialization, tissue alignment, collagen fiber maturity, and large capillary-sized blood vessels compared to the control group (Hashemnia et al. 2019). In another study, Marchianti et al. (2021) investigated the effectiveness of different M*m* (*Lour.*) gel formulations on wound healing in diabetic rats. Histopathology observation, VEGF expression, and hydroxyproline levels showed a significant acceleration of wound healing in all treatment groups compared to the negative control group. The study concluded that all M*m* (*Lour.*) gel formulations

were effective in restoring the delayed healing process on wounds in diabetic rats and were equally effective in accelerating wound healing. Among the formulations, sodium carboxymethyl cellulose (CMC) Na was found to be the most preferable because it did not cause any irritation. Therefore, M*m* (*Lour.*) gel formulations could be considered a promising option for wound healing in diabetic patients (Marchianti et al. 2021). Due to their beneficial properties and other positive effects, medicinal plants are now being used to treat DWs problems and may serve as potential alternatives to the conventional anti-diabetic medications in the future. Many modern phytomedicines have been developed based on traditional medicinal plants (Ansari et al. 2022a). The formulation of phytomedicines may be either single or poly-herbal. Several marketed poly-herbal formulations including Angipars (Res and I-iii 2011), WinVivo (Ongarora 2022), Jathyadi Thailam, Jatyadi Ghritam (Mandrika et al. 2021), and others have been employed to heal DWs. These products are typically composed of individual ingredients sourced from different anti-diabetic herbs, and often come with instructions on dietary modifications, exercise, and rest. These adjustments can ultimately aid patients in re-establishing a healthy lifestyle (Petchi et al. 2014). Medicinal plants and their active constituent responsible for diabetic wound-healing effect are summarized in Table 3.

Naturally isolated compounds-based treatment strategy in diabetic wound healing The theory behind the potential of natural isolated compounds for diabetic wound healing lies in their ability to target various biological pathways involved in the wound-healing process. In diabetic individuals, wound healing is often impaired due to several factors, including poor blood flow, increased oxidative stress, and chronic inflammation. Natural isolated compounds were found to have antioxidant and anti-inflammatory properties, which can help to reduce oxidative stress and inflammation in the wound bed, allowing for more efficient healing. Additionally, these compounds have been found to stimulate angiogenesis, which is important for the formation of new blood vessels to supply oxygen and nutrients to the wound. Furthermore, these compounds have been found to promote collagen deposition, which is necessary for the formation of new tissue in the wound bed. Collagen is a major component of the ECM and is essential for the structural integrity of the skin (Agyare et al. 2019). For instance, Ahmad et al. (2017) found that quercetin has a hypoglycemic effect in STZ-induced diabetic rats and normalized plasma lipids and protein profiles. Additionally, when applied topically to the wound area, quercetin also showed an excellent wound-healing property in diabetic rats. Overall, these findings suggested that quercetin may have potential therapeutic benefits for diabetes management and wound healing (Ahmad et al. 2017)**.** Moreever, Lodhi et al. (2013), evaluated the wound-healing properties of flavonoid-rich fraction and pongamol from *Tephrosia purpurea* (TPF) in diabetic rats. Ointments of pongamol and flavonoid-rich fraction were prepared and applied to excision wounds in STZ-induced diabetic animals. The results showed that percent wound contraction were observed significantly ($p < 0.01$) greater in MAF fraction and 0.5% w/w of luteolin treatment groups. Presence of matured collagen fibers and fibroblasts with better angiogenesis were observed in histopathological studies (Lodhi et al. 2013)**.** Shao et al. (2019) suggested that *Plumbagin* administration can enhance wound-healing activity and serve as a potent anti-diabetic and anti-inflammatory agent in diabetic rats. The diabetic rats showed delayed wound healing, decreased epithelialization, collagen and protein content, reduced serum insulin levels, increased glucose and lipid levels, lowered antioxidant levels, and upregulated levels of inflammatory markers. *Plumbagin* treatment resulted in increased epithelialization, collagen deposition, increased serum insulin levels, increased antioxidant status, lowered lipid peroxides and lipid levels, lowered inflammatory markers, and increased growth factors' expressions. Therefore, *Plumbagin* could be a potential therapeutic agent for the treatment of diabetes and wound healing (Shao et al. 2019). In another study, Chen et al. (2021) indicated that luteolin, when administered, had the potential to improve the delayed wound-healing process in streptozotocin induced diabetic rats. The positive impact of luteolin on wound healing was attributed to its anti-hyperglycemic, anti-inflammatory, and anti-oxidative properties. The study also delves into the underlying mechanisms through which luteolin exerted its effects, such as the inhibition of NF-κB expression, leading to the down-regulation of inflammatory mediators, and the activation of nuclear-related factor-2 (Nrf-2) phosphorylation, resulting in the upregulation of antioxidant enzymes. Furthermore, the study provided biomarkers that may help in determining the status of recovery in diabetic wound healing, such as angiogenesis and neuronal regeneration. Overall, the study highlighted luteolin's potential as a therapeutic agent for treating diabetic wound injury (Chen et al. 2021). The naturally isolated compounds have been found to promote wound healing by stimulating the migration of cells, re-epithelialization, angiogenesis, increase growth factors, reduced inflammation, collagen deposition, and new tissue formation. Table 4 provides a summary of recent *in-vitro* and *In-vivo* studies that have investigated the diabetic wound-healing properties of various naturally isolated compounds by oral/topical route administration.

Green-synthesized nanoparticle-based treatment strategy in diabetic wound healing Nanoparticle-based treatments have gained significant attention in the field of wound healing due to their unique properties, such as high surface area-to-volume ratio, size, and surface chemistry. One promising

Table 3 Summarizes the medicinal plants and their active constituents responsible for the healing effects on DWs reported in the last 11 years (2012–2023)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
1	*Globularia arabica*	Plantaginaceae	Leaves	Methanolic extract	Hexadecanoic acid, L-linalool, Geraniol, Quercetin, Flavone, Gallic acid, Catechol, 1,2-Benzenedicarboxylic acid-bis and Pinene	1, 5, and 10%	15 days	Topical	↑ hydroxyproline content; ↑ IL-6 levels; ↑ wound contraction; ↑ collagen deposition; ↓ inflammatory markers; ↑ cell migration	STZ-induced diabetic rats (60 mg/kg)	Alsarayreh et al. (2022)
2	*Rhus coriaria* L	Anacardiaceae	Fruit	Methanolic extract	Myricetin-3-rhamnoside, Myricetin-3-glucoside, Quercetin 3-O-alpha-L-rhamnopy, Kaempferol, Gallic Acid, Methyl gallate, and Amentoflavone	1, 5, and 10%	15 days	Topical	↓ IL-6 levels; ↑ IL-10 levels; ↑ hydroxyproline content; ↑ wound contraction; ↑ Collagen deposition; ↑ neovascularization; ↑ epithelialization; ↓ inflammatory markers	STZ-induced diabetic rats (60 mg/kg)	Alsarayreh et al. (2021)
3	*Neolamarckia cadamba*	Rubiaceae	Stem and bark	Ethanolic extract	Alkaloids, Flavonoids, Phenols, Saponins, Steroids, Glycosides, Tannins	200, 400 mg/kg, and 5%, 10%	16 days	Oral and Topical	↓ serum glucose level; ↓ inflammatory markers; ↓ NO, MDA, hexosamine; ↑ collagen, total protein; ↑ DNA, SOD, CAT; ↑ re-epithelialization; ↑ vascularization; ↑ wound contraction	STZ-nicotinamide induced diabetic rats (55 mg/kg and 120 mg/kg)	Yadav et al. (2022b)
4	*Olea europaea*	Oleaceae	Leaves and stem	Ethanol/acetone extract	Benzoic acid, 4-formyl-methyl ester, Linoleic acid ethyl ester, Ethyl Oleate, and dl-α-Tocopherol	1:3 w/v	13 days	Oral and Topical	↑ wound contraction; ↑ re-epithelialization; ↑ Collagen deposition; ↓ inflammation; ↑ collagen deposition	Alloxan monohydrate induced diabetic rats (100 mg/kg)	Elnahas et al. (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
5	*Salvia kronenburgii* and *Salvia euphratica var. euphratica*	Lamiaceae	Aerial parts	Ethanolic extract	Phenolic and Flavonoid content	0.5 and 1% w/w	14 days	Topical	↓ inflammation; ↑ angiogenesis; ↑ re-epithelialization; ↑ wound contraction; ↓ oxidative stress; ↑ collagen deposition	STZ- induced diabetic rats (45 mg/kg)	Güzel et al. (2019)
6	*Moringa oleifera*	*Moringaceae*	Leaves	Methanolic extract	Thymine, Octadecanoic acid, d- alpha -Tocopherol, Malonic acid, n-Decanoic acid, Phytol, and Benzyl beta-d-glucoside	10 and 20%	20 days	Topical	↑ wound contraction; ↑ re-epithelialization; ↑ collagen deposition; ↑ VEGF and TGF-β1; ↓ inflammation	STZ-nicotinamide induced diabetic rats (60 mg/kg and 120 mg/kg)	Al-Ghanayem et al. (2022)
7	*Syzygium aromaticum* (Clove)	Myrtaceae	Flower	Ethanolic extract	Eugenol, Caryophyllene, 3-Allyl-6-methoxyphenyl acetate, α-sitosterol, Butanoic acid, and Caryophyllene oxide	2, 4, 6,8 and 10 µg/mL	18 days	Topical	↓ oxidative stress; ↓ wound infection; ↑ wound contraction; ↑ re-epithelialization; ↑ collagen deposition	STZ-induced diabetic rats (65 mg/kg)	Ali et al. (2022)
8	*Combretum molle*	Combretaceae	Leaves	Methanolic extract	lignin, gallic acid, and ellagic acid	Extract feed	4 weeks	Oral	↓ oxidative stress; ↓ inflammation; ↑ wound contraction; ↑ re-epithelialization; ↑ collagen deposition	STZ-induced diabetic rats (50 mg/kg)	Hamza et al. (2021)
9	*Myrtus communis*	Myrtaceae	Berry	Aqueous Extract	Flavonoids, α-terpineol, Myrtenyl acetate, and limonene	6%	3 weeks	Topical	↓ inflammation; ↑ wound contraction; ↑ re-epithelialization; ↑ collagen deposition	STZ-induced diabetic rats	Khodaie et al. (2020)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
10	*Terminalia chebula*	*Combretaceae*	Seeds	Methanolic extraction	Carbohydrate, Alkaloids, -Ssteroids, Saponins, Tannins, Flavonoids, Phenols, Lipids and Proteins	200 and 400 mg/kg	13 days	Oral	↑ superoxide dismutase; ↑ NO level; ↓ lipid peroxidation; ↑ wound contraction; ↓ inflammation	STZ-induced diabetic mice (50 mg/kg)	Singh et al. (2017)
11	*Stryphnodendron adstringens*	Fabaceae	Bark	Alcoholic extract	Gallic acid, rutin and caffeic acid	5%	16 days	Topical	↓ oxidative stress; ↑ re-epithelialization; ↑ angiogenesis; ↓ inflammation; ↑ wound contraction	STZ-induced diabetic rats (80 mg/kg)	De Souza de Aguiar et al. (2021)
12	*Euphorbia hirta linn*	Euphorbiaceae	Leaves	Ethanolic extract	Gallic acid and quercetin	100, 200, 400 mg/ kg and 5, 10%	16 days	Oral and topical	↓ serum glucose level; ↓ plasma level; ↓ NO, MDA; ↓ inflammation; ↑ re-epithelialization; ↑ wound contraction	Alloxan monohydrate induced diabetic rats (120 mg/kg)	Tuhin et al. (2017)
13	*Aloe Vera, Henna, Adiantum capillus-*veneris, and *Myrrha*	Asphodelaceae, Lythraceae, Pteridaceae, and Burseraceae	Leaves and Shoots	Herbal mixture	–	–	21 days	Topical	↓ MMP-9; ↑ angiogenesis; ↓ inflammation; ↑ re-epithelialization; ↑ wound contraction; ↑ collagen deposition	STZ-induced diabetic rats (60 mg/kg)	Galehdari et al. (2016)
14	*Azadirachta indica*	Meliaceae	Leaves	Hydroalcoholic extract	Flavonoids, coumarins, reducing sugars, glycosides, proteins, and fatty acids	80 g w/v, + 1 mL/ injury/day	14 days	Topical	↓ inflammation; ↑ wound contraction; ↑ re-epithelialization; ↑ collagen deposition; ↑ angiogenesis	Alloxan monohydrate induced hyperglycemic rats (45 mg/kg)	Silva et al. (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
15	*Teucrium polium*	Lamiaceae	Aerial	Hydroalcoholic extract	Gallic acid, caffeic acid, chlorogenic acid catechin, rutin, luteolin, quercetin and apigenin	5, 10 and 15%	21 days	Topical	↑ wound contraction; ↑ angiogenesis; ↑ fibroblast proliferation; ↑ collagen deposition; ↑ maturation; ↑ re-epithelialization; ↓ inflammation	STZ-induced diabetic rats (55 mg/kg)	Salih et al. (2020)
16	*Gynura procumbens*	Asteraceae	Leaves	Ethanolic extract	Quercetin, kaempferol, and stigmasterol	0.5%	16 days	Topical	↑ wound contraction; ↓ inflammation; ↑ angiogenesis; ↑ EGF, FGF, VEGF; ↑ cell migration; ↑ fibroblasts, keratinocytes; ↑ mast cells	STZ-induced diabetic mice (100 mg/kg)	Sutthammikorn et al. (2021)
17	*Globularia arabica*, *Malva sylvestris* and *Rhus coriaria*	Plantaginaceae, Malvaceae and Anacardiaceae	Leaves and fruits	Methanolic extracts	Flavonoids and tannins	100 and 200 mg/kg	15 days	Oral	↑ wound contraction; ↑ fibroblasts proliferation; ↑ cell migration; ↓ inflammation; ↑ angiogenesis	STZ-induced diabetic rats (65 mg/kg)	Al Sarayreh et al. (2022)
18	*Acacia auriculiformis* Benth	Fabaceae	Leaves	Methanolic and butanolic extracts	Quercetin, stigmasterol, upeol, and β-sitosterol	200 and 400 mg/kg)	15 days	Topical	↑ collagen deposition; ↑ re-epithelialization; ↓ α-glucosidase enzyme; ↓ α-amylase enzyme; ↓ inflammation; ↑ wound contraction	STZ-nicotinamide induced diabetic rats (50 mg/kg and 120 mg/kg)	Naresh Kumar Rangra and Subir Samanta (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
19	*Helichrysum italicum*	Asteraceae	Flower	Hydro distillation extraction	α-pinene, β-pinene, α-phellandrene, γ-terpinene, p-cymene and cis-α-bergamotene	0.5%	21 days	Topical	↑ hydroxyproline content; ↑ wound contraction; ↑ collagen deposition; ↑ re-epithelialization; ↓ inflammation	STZ-induced diabetic rats (50 mg/kg)	Andjić et al. (2021)
20	*Quercus infectoria*	Fagaceae	Nutgalls	Ethanolic extract	Gallic acid and catechin	30% w/v	14 days	Topical	↑ cell proliferation; ↑ re-epithelialization; ↑ granulation tissue; ↑ collagen deposition; ↓ inflammation; ↓ oxidative stress; ↑ wound contraction	STZ-induced diabetic rats (50 mg/kg)	Chokpaisarn et al. (2017)
21	*Pteris vittata* L	Pteridaceae	Fronds	Aqueous and ethanolic extract	Flavonoids and phenolic	100 µl	15 days	Oral	↑ wound contraction; ↑ collagen deposition; ↑ hydroxyproline content; ↑ hexosamine, VEGF-1; ↓ lipid peroxidation; ↑ MMP-9, Collagenase-2; ↓ TNF-α, IL-6, ROS; ↑ angiogenesis	STZ-induced hyperglycemic rats (40 mg/kg)	Paul et al. (2020)
22	*Smallanthus sonchifolius*	Asteraceae	Leaves	Aqueous extract	Terpenoid, flavonoids, Tannin and phenolic component	0.45 and 150 mg/kg)	14 days	Oral and topical	↑ wound contraction; ↑ collagen deposition; ↑ granulation tissue; ↑ angiogenesis; ↓ inflammation	STZ-nicotinamide induced diabetic rats (45 mg/kg and 110 mg/kg)	Herowati et al. (2018)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
23	*Buddleja polystachya* fresen	Scrophulariaceae	Leaves	Methanolic extract and solvent fraction	Ursolic acid, luteolin, 1 (4-hydroxyphenyl) ethanol ester of docosanoic, isobenzofuranone derivative, and luteolin	5 and 10%	18 days	Topical	↑ wound contraction; ↑ re-epithelialization; ↑ collagen deposition; ↑ angiogenesis; ↓ inflammation	STZ-induced diabetic mice (150 mg/kg)	Getahun et al. (2021)
24	*Pimpinella anisum*	Apiaceae	Seeds	Methanolic extract	Eugenol, methyl chavicol, flavonoids and polyenes	10%	21 days	Topical	↑ fibroblasts deposition; ↑ wound contraction; ↓ lymphocytes; ↑ number of fibrocytes; ↑ re-epithelialization; ↑ collagen deposition; ↑ hydroxyproline content; ↓ MDA, glutathione; ↓ oxidative stress	STZ-induced diabetic mice (60 mg/kg)	Hashemnia et al. (2019)
25	*Terminalia bellerica*	Combretaceae	Fruit	Ethanolic extract	β-sitosterol, gallic acid, ellagic acid, chebulagic acid, mannitol	200 and 400 mg/kg	20 days	Oral	↑ wound contraction; ↑ re-epithelialization; ↑ scar residue formation; ↑ hydroxyproline content; ↓ inflammation	STZ-induced diabetic rats (60 mg/kg)	Singh et al. (2020)
26	*Passiflora edulis*	Passifloraceae	Leaves	Ethanolic/ water extract fractionation	Isoorientin, apigenin-6–8-di-C-glycoside, luteolin-7-O-pyranosyl-3-O-glycoside, apigenin-6-C-arabinoside-8-C-glycoside and quercetin	0.36 mL	14 days	Topical	↓ oxidative stress; ↑ MDA, SOD; ↑ collagen deposition; ↓ inflammation; ↑ wound contraction; ↑ lipid peroxidation	Alloxan monohydrate induced diabetic mice (130 mg/kg)	Soares et al. (2020)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
27	*Epiphyllum oxypetalum*	Cactaceae	Leaves	Ethanolic extract	–	10 and 20%	14 days	Topical	↑ wound contraction; ↑ fibroblasts deposition; ↑ macrophage deposition; ↓ inflammation	STZ-induced diabetic mice (60 mg/kg)	Dwita et al. (2019)
28	*Lepidium meyenii*	Brassicaceae	Roots	Hydroalcoholic extract	Benzyl glucosinolates	5, 10% and 200 mg/kg	21 days	Topical	↓ bacterial count; ↑ hydroxyproline content; ↑ hexosamine content; ↑ granulation tissue; ↑ wound contraction	STZ-induced diabetic rats (50 mg/kg)	Bramara et al. (2017)
29	*Pterocarpus marsupium*	Fabaceae	Heartwood	Aqueous extract	Phenolic, essential oils, alkaloids and flavonoids	0.4, 0.8 and 1.2% w/v	18 days	Topical	↑ collagen deposition; ↑ re-epithelialization; ↓ inflammatory cells; ↑ angiogenesis; ↑ wound contraction; ↑ granulation tissue	STZ-induced diabetic rats (65 mg/kg)	Manne et al. (2021)
30	*Lepidium sativum*	Brassicaceae	Seed oil	–	Propanoic acid, citronellol, palmitic acid, linoleic acid and geraniol	100 mg	5 days	Topical	↑ angiogenesis; ↑ re-epithelialization; ↓ TNF-α and MMP-9; ↑ VEGF level; ↓ inflammation; ↑ wound contraction	Alloxan monohydrate induced diabetic rats (65 mg/kg)	Kamel et al. (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
31	*Selaginella bryopteris* Linn	Selaginaceae	–	Ethanol/petroleum ether (Flavonoid-enriched fraction)	Catechine, L-fucitol, lupeol, amentoflavone, gallic acid, imidazole, palmitic acid, and myo-inositol	0.5 and 0.10% w/w	15 days	Topical	↑ epithelialization; ↑ wound contraction; ↓ TNF-α, IL-2, IL-6; ↑ CAT, SOD, MDA, GSH; ↑ pro-apoptotic-53 (p-53); ↑ caspase-3, caspase-9; ↓ inflammation	STZ-induced diabetic rats (60 mg/kg)	Gautam et al. (2023)
32	*Urtica dioica* and *Lavandula angustifolia*	Urticaceae and Lamiaceae	Whole	Ethanolic extract	Caffeic acid, rutin, isoquercetin, syringic acid, quercetin, kaempferol and apigenin derivatives	100 µL, 10MRSA and 10MSSA	–	–	↓ bacterial infection; ↑ wound contraction; ↑ re-epithelialization; ↓ inflammation	Diabetic foot ulcers	Zenão et al. (2017)
33	*Plantago major*	Plantaginaceae	Wholes plants	Ethanolic extract	Ursolic acid and oleanolic acid	0.5 g	21 days	Topical	↑ epithelialization; ↑ fibroblast proliferation; ↑ wound contraction; ↓ inflammation; ↓ NO production; ↑ migration of fibroblast	Alloxan monohydrate induced hyperglycemic rats (60 mg/kg)	Kartini et al. (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
34	*Aloe vera* (L.) Burm. f., *Aloe arborescens* Mill., *Aloe eru A. Berger*, Aloe *grandidentata* Salm-Dyck, *Aloe perfoliata* L., *Aloe brevifolia* Mill., *Aloe saponaria* Haw. and *Aloe ferox* Mill	Asphodelaceae	Leaves	Methanolic extract	Aloesin (aloeresin B), Chrysoeriol-7-O-glycuronyl, Aloenin B, Isovitexin (6-C-glucosyl-apigenin) and Luteolin-O-xylosylglucoside	250 mg/kg	10 days	Topical	↓ inflammation; ↑ wound contraction; ↑ collagen deposition; ↑ angiogenesis	STZ-induced diabetic rats (70 mg/kg)	El Sayed et al. (2016)
35	*Piper crocatum* Ruiz & Pav	Piperaceae	Leaves	Methanolic extract and fractionation	Glacial acetic acid	5%	72 h	-	↑ wound closure; ↑ collagen deposition; ↑ cell migration; ↑ p53, aSMA, E-cadherin; ↑ SOD1 level	Hyperglycemic fibroblasts	Setyawati et al. (2021)
36	*Centella asiatica, Cucuma longa, Zingiber cassumunar, Garcinia mangostana, Zingiber officinale, Ewingella americana, Piper nigrum, Sarracenia alata,* and *Areca catechu*	Apiaceae, Zingiberaceae, Zingiberaceae, Guttiferae, Zingiberaceae, Yersiniaceae, Piperaceae, Sarraceniaceae and Fabaceae	Leaves, Rhizome, Rhizome, Peel, Rhizome, Rhizome, Seed, Leaves and fruit	Ethanolic extract	–	5–50 mM	24 h	-	↑ TIMP-1, VEGF, TGF-b; ↓ TNF-a, IL-6, MMP-9; ↑ restore the keratinocytes; ↑ wound closure; ↓ inflammation; ↓ bacterial infection	HaCaT cells diabetic foot ulcers	Chumpolphant et al. (2022)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
37	*Teucrium polium and Aloe vera* (L.)	Lamiaceae and Asphodelaceae	Leaves	Hydroethanolic extract	Phenolic and flavonoid content	5 and 10% w/w	14 days	Topical	↑ cell proliferation; ↓ MDA, TNF-α, IL-1β; ↑ fibroblasts proliferation; ↑ collagen deposition; ↑ VEGF, IGF-1, GLUT-1; ↓ inflammatory markers; ↑ wound contraction	STZ-induced diabetic mice (55 mg/kg)	Gharaboghaz et al. (2020)
38	*Helichrysum italicum (Immortelle)*	Asteraceae	Oil	–	Monoterpenes, sesquiterpene, γ-curcumene, and β-selinene	0.5 g	21 days	Topical	↑ hydroxyproline content; ↑ collagen deposition; ↑ re-epithelialization; ↑ scar maturation; ↓ inflammation; ↑ wound contraction	STZ- induced diabetic rats (50 mg/kg)	Andjić et al. (2022)
39	*Angelica dahurica*	Apiaceae	–	–	Isoimperatorin, bergapten, oxypeucedanin hydrate, and oxypeucedanin	1.8 g/kg	14 days	Oral	↑ wound closure; ↑ neovascularization; ↑ pDGF-β expression; ↑ capillary formation; ↓ inflammation; ↑ angiogenesis; ↑ HIF-1α synthesis	Diabetic db/db mice	Guo et al. (2020)
40	*Piper betel*	Piperaceae	Leaves	Aqueous extract	Flavonoids, carbohydrate, amino acids, tannins and terpene	50 mg/kg	7 days	Topical	↓ oxidative stress; ↓ 11β HSD-1 expression; ↑ hydroxyproline content; ↑ SOD, 11b-HSD-1; ↑ wound closure; ↓ MDA level	STZ-induced diabetic rats (45 mg/kg)	Ghazali et al. (2016)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
41	*Datura metel* L	Solanaceae	Leaves	Petroleum ether, chloroform, ethyl acetate, and methanolic extracts	Phytol, Silicone oil, Neophytadiene, Flavonoids, Phenols and Glycosides	50 mg/mL	24 h	–	↓ inflammation; ↓ bacterial infection; ↑ wound closure; ↓ anti-diabetic; ↓ antioxidant	Diabetic fibroblast	Prasathkumar et al. (2022)
42	*Sida cordifolia* Linn	Malvaceae	aerial	Methanolic and hydroalcoholic extracts	Gallic acid, flavonoids and carbohydrates	–	20 days	Topical	↑ wound contraction; ↑ collagen deposition; ↑ epithelialization; ↑ hydroxyproline content; ↑ epithelial cells; ↓ inflammation	STZ-induced diabetic rats (40 mg/kg)	Pawar et al. (2016)
43	*Aster koraiensis*	Asteraceae	Aerial	Ethyl alcohol extract	–	100 mg/kg	14 days	Oral	↑ re-epithelialization; ↑ keratinocyte level; ↑ wound contraction; ↑ MMP-2, MMP-9; ↓ inflammation; ↑ skin tissue	STZ-induced diabetic rats (75 mg/kg)	Hyun et al. (2018)
44	*Merremia mammosa* Lour	Convolvulaceae	Simplicia	Ethanolic extract and fractionation	Merremosida, flavonoids and mammoside	0.5 and 10%	14 days	Topical	↑ hydroxyproline content; ↑ VEGF levels; ↓ inflammation; ↑ collagen deposition; ↑ angiogenesis; ↑ wound contraction	STZ-induced diabetic rats (40 mg/kg)	Marchianti et al. (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
45	*Annona reticulata* L	Annonaceae	Leaves	Ethanolic extract	Quercetin and β-sitosterol	10% and 150 mg/kg	14 days	Topical	↑ cell proliferation; ↑ cell migration; ↑ skin fibroblast; ↑ wound contraction; ↑ keratinocytes level; ↑ TGF-b, CTGF, VEGF; ↓ inflammatory markers; ↑ a-SMA, MMP-2, MMP-9; ↑ collagen-1, collagen-3	STZ-induced diabetic mice (40 mg/kg)	Mazumdar et al. (2021)
46	*Solidago chilensis*	Asteraceae	Leaves	Hydroalcoholic extract	Monoterpenes, sesquiterpenes, diterpenes, flavonoids (quercetin and rutin)	10%	21 days	Topical	↓ inflammatory infiltrate; ↑ angiogenesis; ↑ collagen-1, MMP-2; ↓ collagen-3, MMP-9; ↑ wound contraction	Alloxan monohydrate induced diabetic rats (32 mg/kg)	Moreira et al. (2021)
47	*Blepharis maderaspatensis* (L.)	Acanthaceae	Leaves	Ethanolic extract	–	10, 15 and 20% w/w	23 days	Topical	↑ wound contraction; ↓ inflammation; ↑ tissue formation; ↓ bacterial infection	STZ-induced diabetic (45 mg/kg)	Jacob et al. (2017)
48	*Curcuma longa*	Zingiberaceae	Rhizome	Methanolic and ethanolic extract	Gallic acid and phenols	1:1 w/w	9 days	Oral	↓ bacterial infection; ↑ wound contraction; ↓ inflammation; ↑ glucose tolerance; ↑ tissue formation	Alloxan monohydrate induced diabetic mice (150 mg/kg)	Khan et al. (2019)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
49	*Jatropha Neopauciflora*	Euphorbiaceae	Latex	Fraction	Gallic acid, catechin, quercetin, carbohydrate and proteins	50,75 and 100%	10 days	Topical	↑ fibroblasts deposition; ↓ oxidative stress; ↑ wound healing; ↓ inflammation; ↓ microbial infection	STZ-induced diabetic mice (150 mg/kg)	Hernandez-Hernandez et al. (2021)
50	*Salvia euphratica*	*Lamiaceae*	Aerial	Ethanolic extract	Flavonoids, phenolic and terpenoids	1% w/w	14 days	Topical	↑ fibroblasts deposition; ↑ collagen deposition; ↓ inflammation; ↑ skin tissue formation; ↑ wound contraction	STZ-induced diabetic rats; (45 mg/kg)	Gökalp Özkorkmaz (2018)
51	*Olea europaea L*	Oleaceae	Leaves	Aqueous extract	Oleuropein	0.9%	21 days	Topical	↑ collagen deposition; ↓ inflammation; ↑ skin tissue formation; ↑ wound contraction	STZ-induced diabetic rats (60 mg/kg)	Samancıoğlu et al. (2016)
52	*Binahong*	Basellaceae	Leaves	Ethanolic extract	Flavonoids, oleanolic acid, protein, ascorbic acid. and saponins	1:3 ratio	4 days	Topical	↑ granulation tissue; ↑ epithelialization; ↑ wound contraction; ↑ collagen deposition; ↓ inflammation	Diabetic patients	Merbawani et al. (2019)
53	*Psidium guajava* Linn	Myrtaceae	Leaves	Tannin enriched fraction	Gallic acid and tannin	5, 10 and 90%	12 days	Topical	↑ epithelialization; ↑ wound contraction; ↑ collagen deposition; ↓ inflammation; ↑ tissue formation	Alloxan monohydrate induced diabetic rats (84 mg/kg)	Kumari et al. (2018)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
54	*Calotropis procera*	Apocynaceae	Root and bark	Ethanolic extract	Flavonoids, alkaloids and tannins	5% w/w and 100, 200 mg/kg)	16 days	Oral	↑ epithelialization; ↑ tissue formation; ↑ wound contraction; ↑ collagen deposition; ↓ inflammation	STZ- induced diabetic rats (65 mg/kg)	Mali et al. (2020)
55	*Centella asiatica* L	Apiaceae	Simplicia herbs	Ethanolic extract	Tannins, saponins, and steroids	3, 5 and 7%)	21 days	Topical	↑ collagen deposition; ↑ epithelialization; ↑ tissue formation; ↑ wound contraction; ↓ inflammation	STZ- nicotinamide induced diabetic mice (120,150 and 180 mg/Kg), (70 mg/kg)	Rohmayanti and Hapsari (2021)
56	*Mangifera indica*	Anacardiaceae	Bark	Ethanolic extract	Coumarins, flavonoids, tannins, steroids and saponins	Extract application	18 days	Topical	↑ granulation tissue; ↑ scar formation; ↓ inflammation; ↑ collagen deposition; ↑ blood vessels formation	Alloxan monohydrate induced diabetic rats (100 mg/kg)	Ajani and Olateju (2020)
57	*Homalomena pineodora*	Araceae	Leaves	Hydrodistillation	2-undecanone, 4-tridecanone, 2-decylcyclopentanone, heptadecane-2,4-dione and vinyl decanoate	8 g	24 h	Topical	↓ microbial infection; ↓ inflammation; ↓ growth reduction; ↑ wound dressing	Isolated diabetic wound ulcer	Rozman et al. (2018)
58	*Ichnocarpus frutescens, Ficus dalhousiae, Crateva magna, Alpinia galanga,* and *Swertia chirata*	Apocynaceae, Moraceae, Capparaceae, Zingiberaceae and Gentianaceae	Polyherb	Infusion extract	–	5 and 10%	21 days	Topical	↑ epithelialization; ↑ wound contraction; ↑ collagen deposition; ↓ inflammation	STZ-nicotinamide induced diabetic mice (55 mg/kg)	Quazi et al. (2022)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
59	*Orthosiphon aristatus*	Lamiaceae	Leaves	Ethanolic and aqueous extract	Rosmarinic acid, sagerinic acid, lithospermic acid, betulinic acid, eupatorin, tetramethylscutellarein and pillion	1 g/kg and 100 µg/mL	28 days	Oral	↓ blood glucose level; ↑ lipid profile level; ↑ epithelialization; ↑ wound contraction; ↓ oxidative stress; ↓ inflammatory infection	STZ- induced diabetic rats	Abdullah et al. (2020)
60	*Hypericum Perforatum*	Hypericaceae	Flowering aerial part	Olive oil extract	Naphthodianthrones, phloroglucinols, flavonoids, bioflavonoids, and phenylpropanoids	1.25 mL/kg	21 days	Topical	↑ hydroxyproline content; ↓ inflammation; ↑ collagen deposition; ↑ angiogenesis; ↑ epithelialization; ↑ wound contraction; ↑ fibroblastic formation	STZ-induced diabetic rats (30 mg/kg)	Altıparmak and Eskitaşçıoğlu (2018)
61	*Salvia hypargeia* Fisch	Lamiaceae	Aerial part	Ethanolic extract	Flavonoids, phenolic, and terpenoids	0.5 and 1%	14 days	Topical	↑ re-epithelialization; ↑ granulation tissue; ↑ wound contraction; ↓ hydroxyproline content; ↑ GSH level	STZ-induced diabetic rats (45 mg/kg)	Ozay et al. (2021)
62	*Cinnamomum*	Lauraceae	Bark	Hydroethanolic extract	Epicatechin, quercetin, hydroxyl cinnamaldehyde, cinnamyl alcohol, cinnamaldehyde, 2-methoxy cinnaldehyde and eugenol	5 and 10%	14 days	Topical	↑ keratin biosynthesis; ↑ re-epithelialization; ↑ fibroblast proliferation; ↓ inflammation; ↑ collagen deposition; ↑ wound contraction; ↑ blood vessels; ↑ cell proliferation	STZ-induced diabetic mice (60 mg/kg)	Daemi et al. (2019)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
63	*Citrus sinensis* and *Punica granatum*	Rutaceae and Punicaceae	Peels	Ethanolic extract	Flavonoids, tannins, polyphenols, and quinones	50,100 and 200 mg/kg	12 days	`	↑ re-epithelialization; ↑ granulation tissue; ↑ wound contraction; ↓ inflammation; ↓ bacterial infection	Alloxan monohydrate induced diabetic rats (125 mg/kg)	Sovia (2021)
64	*Lycium depressum*	Solanaceae	Leaves	Methanolic extract	Gallic acid, flavonoid and catechin	1,2 and 4 g	21 days	Topical	↑ wound contraction; ↓ epithelialization time; ↓ inflammation; ↑ hydroxyproline content; ↑ scar residue formation	STZ-induced diabetic rats (50 mg/kg)	Naji et al. (2017)
65	*Teucrium polium*	Lamiaceae	Aerial part	Ethanolic extract	Gallic acid	2, 3, 4,5 and 10%	21 days	Topical	↑ granulation tissue; ↑ re-epithelialization; ↑ wound contraction; ↓ inflammation; ↓ bacterial infection	Alloxan monohydrate induced diabetic rats (125 mg/kg)	Fallah Huseini et al. (2020)
66	*Anthocephalus Cadamba*	Rubiaceae	Leaves	Aqueous extract	Flavonoids, saponins, and terpenoids	5% and 500 mg/kg	21 days	Topical	↑ epithelial regeneration; ↑ neovascularization; ↑ wound contraction; ↑ VEGF level; ↓ inflammation; ↑ collagen deposition; ↑ fibroblast proliferation	STZ-induced diabetic rats (60 mg/kg)	Ali et al. (2021)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
67	*Caesalpinia bonducella* and *Cyclea peltata*	Fabaceae and Menispermaceae	Leaves, bark, root and aerial part	Ethyl acetate and methanolic extract	–	50 and 100 mg/kg	15 days	Topical	↑ re-epithelialization; ↑ granulation tissue; ↑ wound contraction; ↓ inflammation; ↓ bacterial infection	STZ-induced diabetic rats (40 mg/kg)	Jagadeep Chandra et al. (2017)
68	*Jasminum grandiflorum* Linn	Oleaceae	Flowers	Ethanolic extract	Flavonoid, steroid, glycoside, terpenes and resins	250 mg/kg	14 days	Oral	↑ granulation tissue; ↑ re-epithelialization; ↑ hydroxyproline content; ↓ inflammation; ↑ wound contraction	STZ-induced diabetic rats (50 mg/kg)	Almeida et al. (2017)
69	*Helianthus tuberosus* L	Asteraceae	Tubers	Ethyl acetate fraction	Chlorogenic acid, dicaffeoylquinic acid isomer-1, dicaffeoylquinic acid isomer-2 and pinellic acid	25, 50 and 100 g/mL	48 h	–	↓ antioxidant activity; ↓ antidiabetic activity; ↑ wound contraction; ↓ bacterial infection	Fibroblast (NIH3T3) cells	Mariadoss et al. (2021)
70	*Abelmoschus esculentus* (Okra) and *Sargassum duplicatum*	Malvaceae	Fruits	Ethanolic extract	Ascorbic acid and flavonoids	0.3 mL	14 days	Topical	↑ re-epithelialization; ↑ fibrocytes cells; ↑ fibroblasts proliferation; ↑ collagen densities; ↑ wound contraction; ↓ bacterial infection; ↓ neutrophil, macrophages	STZ-high-fat diet induced diabetic mice (30 mg/kg)	Ilmi et al. (2020)
71	*Crocus Pallasii Subsp.* and *Haussknechtii boiss*	Iridaceae	Leaves	Methanolic extract	Gallic acid and catechin	0.1 mL and 1 mg/mL	21 days	Topical	↑ hydroxyproline content; ↓ microbial infection; ↑ wound contraction; ↑ re-epithelialization; ↓ inflammation	STZ-induced diabetic rats (50 mg/kg)	Zadeh et al. (2020)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
72	*Pistacia atlantica*	*Anacardiaceae*	Oil	Hydrodistillation	α-Pinene, camphene, β-myrcene and limonene	250 µl/day	14 days	Topical	↑ VEGF expression; ↑ hydroxyproline content; ↑ angiogenesis; ↓ inflammation; ↑ wound contraction; ↑ re-epithelialization; ↑ collagen turnover	STZ-induced diabetic rats (50 mg/kg)	Shahouzehi et al. (2018)
73	*Strychnos pseudoquina*	Loganiaceae	Stem bark	Hydroethanolic extract	Flavonoids quercetin 3-O-methyl ether and strychnobiflavone	5 and 10%	21 days	Topical	↓ oxidative Status; ↓ inflammation; ↑ blood vessels; ↑ wound contraction; ↑ re-epithelialization; ↑ collagen-I, collagen-III	STZ-induced diabetic rats (60 mg/kg)	Sarandy et al. (2017)
74	*Ginkgo biloba*	Ginkgoaceae	Leaves	Aqueous extract	Myricetin, quercetin, kaempferol, and isorhamnetin	1 and 5%	13 days	Topical	↑ collagen synthesis; ↑ wound contraction; ↑ re-epithelialization; ↓ inflammation; ↓ microbial infection	Alloxan monohydrate induced diabetic rats (130 mg/kg)	Bardaa et al. (2021)
75	*Syzygium mundagam*	Myrtaceae	Bark	Methanolic extract	–	1 and 2%	21 days	Topical	↑ wound contraction; ↑ re-epithelialization; ↑ migration of neutrophils; ↓ inflammation; ↑ collagen fibers; ↑ epidermis formation; ↑ fibroblasts proliferation	STZ-nicotinamide induced diabetic mice (60 mg/kg and 120 mg/kg)	Chandran et al. (2017)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
76	*Moringa oleifera*	*Moringaceae*	Leaves	Aqueous fraction	Flavonoids, tannins, and steroids	0.5, 1 and 2% w/w	21 days	Topical	↓ bacterial infection; ↑ wound contraction; ↑ VEGF level; ↑ tissue regeneration; ↓ inflammatory mediators; ↑ angiogenic marker; ↓ TNF-α, IL-1β, IL-6	STZ-nicotinamide induced diabetic mice (65 mg/kg and 150 mg/kg)	Muhammad et al. (2016)
77	*Pouteria ramiflora*	Sapotaceae	Leaves	Ethanolic extract	Flavonoids, phenol, tannins, and steroids	2%	30 days	Topical	↓ inflammatory cells; ↑ angiogenesis; ↑ wound contraction; ↑ fibroblasts proliferation; ↑ re-epithelialization; ↑ tissue regeneration	STZ-induced diabetic rats (50 mg/kg)	Corrêa et al. (2021)
78	*Eucalyptus alba*	Myrtaceae	Leaves	Ethanolic, methanolic, and acetone extract	P-coumaric acid, kaempferol, salicylic acid, coumarin and quercetin	0.1 mg/mL	24 h	-	↓ antidiabetic activity; ↓ antioxidant activity; ↑ cell proliferation; ↑ wound contraction	Scratch diabetic wound	Mumtaz et al. (2022)
79	*Sphenocentrum jollyanum* pierre	Menispermaceae	Roots and leaves	Aqueous extract	Flavonoids, glycosides, essential oils, saponins and resins	100 and 200 mg/kg	14 days	Topical	↓ TNF-α, IL-6; ↓ microbial colonies; ↑ growth factor secretion; ↑ tissue granulation; ↑ new blood vessels; ↑ wound contraction; ↑ fibroblast proliferation; ↑ collagen deposition	STZ-induced diabetic rats (35 mg/kg)	Adeleke et al. (2022)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
80	*Cotinus coggygria*	Anacardiaceae	Leaves	Ethanolic extract	Gallic acid and atechin	5% w/w	14 days	Topical	↑ wound contraction; ↑ re-epithelialization; ↑ tissue regeneration; ↓ inflammatory mediators; ↑ hydroxyproline content; ↓ malondialdehyde level	STZ-induced diabetic rats (50 mg/kg)	Aksoy et al. (2016)
81	*Hedera nepalensis*	Araliaceae	Leaves	Ethanolic extract	Phenols and flavonoids	Extract feed	14 days	Topical	↓ inflammation; ↓ antioxidant activity; ↑ wound contraction; ↑ re-epithelialization; ↓ blood glucose levels; ↑ tissue regeneration	Alloxan monohydrate induced diabetic rats	Asif et al. (2022)
82	*Pomegranate* (Saudi)	*Lythraceae*	Peels	Methanolic extract	Gallic acid and quercetin	5.0 g and 100 g	21 days	Topical	↑ mRNA, TGF-β1; ↑ EGF, VEGF; ↑ hydroxyproline levels; ↓ NO levels; ↑ wound contraction; ↑ re-epithelialization; ↑ tissue regeneration	Alloxan monohydrate induced diabetic rats (150 mg/kg)	Karim et al. (2021)
83	*Mimosa pudica* L	Fabaceae	Leaves	Ethanolic extract	Phenols and flavonoids	2.5 and 5%	11 days	Topical	↑ wound contraction; ↑ re-epithelialization; ↑ tissue regeneration; ↓ inflammation	STZ-induced diabetic rats (55 mg/kg)	Kumar et al. (2017b)
84	*Piper amalago* L	Piperaceae	Leaves	Aqueous extract	Amide	200 and 500 mg	15 days	Topical	↑ wound contraction; ↑ scar residue formation; ↑ tissue regeneration; ↓ inflammation	Diabetic patient wound	Dos Santos et al. (2020)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
85	*Martynia annua* Linn	Martyniaceae	Leaves	Fraction	Luteolin	0.2 and 0.5% w/w	18 days	Topical	↑ hydroxyproline content; ↑ re-epithelialization; ↑ tissue regeneration; ↑ wound contraction; ↓ inflammation; ↑ collagen deposition	STZ-induced diabetic rats (50 mg/kg)	Lodhi and Singhai (2013a)
86	*Tillandsia recurvata* and *Guaiacum officinale*	Bromeliaceae and Zygophyllaceae	Leaves	Ethanolic extract	_	100 mg/kg	12 days	Topical	↑ wound contraction; ↑ scar residue formation; ↑ tissue regeneration; ↓ inflammation	STZ-induced diabetic rats (65 mg/kg)	Bahado-Singh (2014)
87	*Tephrosia purpurea* Linn	Fabaceae	Aerial	Fraction	Isolonchocarpin and pongamol	0.2 and 0.5% W/W	20 days	Topical	↑ hydroxyproline content; ↑ wound contraction; ↑ SOD, CAT, GSH; ↑ protein content; ↑ collagen fibers; ↓ inflammation; ↑ fibroblasts proliferation; ↑ angiogenesis promotion; ↑ re-epithelialization	STZ-induced diabetic rats (50 mg/kg)	Lodhi et al. (2013)
88	*Annona squamosa*	Annonaceae	Leaves	Ethanolic extract	Gallic acid	100 mg/kg	16 days	Topical	↑ cellular proliferation; ↑ collagen synthesis; ↑ DNA, protein, collagen; ↑ re-epithelialization; ↓ inflammation; ↑ wound contraction	STZ-nicotinamide induced diabetic rats (50 mg/kg and 110 mg/kg)	Ponrasu and Suguna (2012)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
89	*Astragali Radix* and *Rehmanniae Radix*	Leguminosae and Scrophulariaceae	Raw herbs	Aqueous extract	Iridoids, saccharides, amino acid and inorganic ions	0.98 g/kg	8 days	Topical	↑ angiogenesis promotion; ↑ cell migration ↓ reduced inflammation; ↑ tissue formation; ↓ inflammation; ↑ wound contraction; ↑ fibroblast proliferation	STZ-induced diabetic rats (70 mg/kg)	Lau et al. (2012)
90	*Ageratina pichinchensis*	Asteraceae	Aerial part	Aqueous extract	7-O-(β-D-glucopyranosyl)-galactin	40, and 70%	11 days	Topical	↑ wound contraction; ↑ scar residue formation; ↑ tissue regeneration; ↓ inflammation; ↑ angiogenesis promotion	STZ-induced diabetic rats (50 mg/kg)	Romero-Cerecero et al. (2014)
91	*Catharanthus roseus* L	Apocynaceae	Leaves	Methanolic extract	Alkaloids, phenols, flavonoids and saponin	200 and 400 mg/kg	13 days	Topical	↓ blood glucose level; ↑ wound contraction; ↑ collagen fibers; ↓ inflammation	STZ-induced diabetic mice (30 mg/kg)	Singh et al. (2014b)
92	*Curculigo orchioides*	Amarylli-daceae	Root and tubers	Methanolic extract	Phenols, tannins, alkaloids, saponin and flavonoids	200 and 400 mg/kg	13 days	Oral	↑ superoxide dismutase; ↑ nitric oxide level; ↑ wound contraction; ↓ lipid peroxidation; ↓ inflammation; ↑ angiogenesis promotion; ↓ oxidative stress	STZ-induced diabetic mice (50 mg/kg)	Singh et al. (2014a)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
93	*Matricaria Chamomilla*	Asteraceae	Whole part	Hydroalcoholic extract	–	5 and 10%	15 days	Topical	↑ fibroblast proliferation; ↑ re-vascularization; ↓ inflammation; ↑ wound contraction; ↓ bacterial infection	STZ-induced diabetic rats (50 mg/kg)	Nematollahi et al. (2019)
94	*Solanum xanthocarpum*	Solanaceae	Aerial	Ethanolic extract	Chlorogenic acid	5, 10% w/w and 100, 200 mg/kg	14 days	Oral and topical	↑ collagen deposition; ↑ hexosamine level; ↑ hyaluronic acid; ↑ protein, DNA; ↑ wound contraction; ↓ inflammation; ↓ blood glucose level; ↓ lipid peroxidation; ↓ nitric oxide level	STZ-induced diabetic rats (65 mg/kg)	Parmar et al. (2018)
95	*Allium sativum*	Liliaceae	Bulbs	Ethanolic extract	Alkaloids, carbohydrates and flavonoids	1 and 10% w/w	16 days	Topical	↑ wound contraction; ↑ collagen fibers; ↓ inflammation; ↑ re-epithelialization; ↑ scar residue formation	Alloxan monohydrate induced diabetic rats (150 mg/kg)	Zuber et al. (2013)
96	*Hypericum perforatum*	Hypericaceae	Whole plant	Hydroalcoholic extract	Flavonoids, bioflavonoids, and phenylpropanoids	5 and 10%)	15 days	Topical	↑ fibroblast proliferation; ↑ collagen bundles; ↓ inflammation; ↑ wound contraction; ↑ re-vascularization	STZ-induced diabetic rats (50 mg/kg)	Yadollah-Damavandi et al. (2015)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
97	*Ficus mollis*	Moraceae	Bark	Methanolic extract	Flavonoids, phenols and tannins	5 and 10%	16 days	Topical	↓ blood glucose level; ↑ wound contraction; ↑ collagen fibers; ↓ inflammation	Alloxan monohydrate induced diabetic rats (150 mg/kg)	Jameeluddin et al. (2014)
98	*Cinnamomum Tamala*	Lauraceae	Leaves	Ethanolic extract	Tannins and phenolic	0.5% w/v and 100 mg/kg	16 days	Topical	↑ re-epithelialization; ↑ hydroxyproline content; ↑ collagen deposition; ↓ inflammation; ↑ elastin deposition; ↑ wound contraction; ↑ wet & dry granulation	STZ-induced diabetic rats (60 mg/kg)	Soni et al. (2013)
99	*Alternanthera brasiliana*	Amaranthaceae	Leaves	Methanolic extract	Triterpenoids and alkaloids	5% w/w	7 days	Topical	↑ SOD, CAT levels; ↑ wound contraction; ↓ glutathione level; ↓ inflammation; ↑ hydroxyproline content; ↑ protein content	STZ-induced diabetic rats (40 mg/kg)	Barua et al. (2013)
100	*Allium cepa* Linn	Amarylli-daceae	Bulbs	Methanolic extract	_	300, 400 and 500 mg/kg	10 days	Oral	↓ blood glucose level; ↑ wound contraction; ↓ inflammation; ↑ re-epithelialization; ↑ scar residue formation	Alloxan monohydrate induced diabetic mice (120 mg/kg)	Tsala et al. (2015)
101	*Murraya koenigii*	Rutaceae	Leaves	Aqueous extract	Saponins, flavonoids, terpenoids and steroids	200, 300 and 400 mg/kg	24 days	Oral	↓ blood glucose level; ↓ lipid level; ↑ wound contraction; ↓ inflammation; ↑ re-epithelialization	STZ-high-fat diet induced diabetic rats (35 mg/kg)	Vikram Kumar et al. (2012)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
102	*Michelia champaca*	Magnoliaceae	flowers	Ethanolic extract	–	2.5, 5 and 10%	16 days	Topical	↑ wound contraction; ↓ inflammation; ↑ hydroxyproline content; ↑ re-epithelialization	STZ-induced diabetic rats (30 mg/kg)	Gowda et al. (2013)
103	*Carica papaya*	Caricaceae	Fruits	Aqueous extract	Vitamin A and C	200 and 400 mg/kg)	21 days	Oral	↓ bacterial infection; ↑ wound contraction; ↑ granulation tissue; ↑ epithelialization tissue; ↓ inflammation	Alloxan monohydrate induced diabetic rats (150 mg/kg)	Michael et al. (2015)
104	*Momordica charantia*	Cucurbitaceae	Fruits	Aqueous extract	Charantin, vicine, polypeptide-p, saponins, 5-hydroxytryptamine, alkaloids and momordicine	50 mg and 0.9%	10 days	Topical	↑ TGF-β expression; ↑ total protein; ↑ wound contraction; ↑ granulation tissue; ↑ epithelialization tissue; ↓ inflammation	STZ-induced diabetic rats (50 mg/kg)	Hussan et al. (2014)
105	*Melia azedarach L*	Meliaceae	Leaves	Methanolic extract	–	2 and 5%	18 days	Topical	↑ wound contraction; ↑ granulation tissue; ↓ inflammation; ↓ bacterial infection	Alloxan monohydrate induced diabetic rats (120 mg/kg)	Vedha Vijaya et al. (2013)
106	*Byrsonima Crassifolia*	Malpighiaceae	Seeds	Hexane extract	Esters, epicatechins and glycolipids	0.2 and 10% w/w	16 days	Topical	↑ granulation tissue; ↑ hydroxyproline content; ↑ total protein content; ↑ wound contraction; ↓ inflammation; ↓ bacterial infection; ↑ DNA, SOD, CAT level	STZ-induced diabetic rats (50 mg/kg)	Pérez Gutiérrez and Muñiz Ramirez (2013)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
107	*Garcinia kola*	Clusiaceae	Seeds	Extraction and fractionation	Garcinia hydroxybiflavanonol	50 mg/kg and 15, 30%	8 days	Topical	↑ re-epithelialization; ↑ granuloma tissue; ↑ hydroxyproline content; ↑ wound contraction; ↓ MDA levels	STZ-induced diabetic rats (60 mg/kg)	Nwaehujor et al. (2013)
108	*Ocimum sanctum*	Lamiaceae	Leaves	Ethanolic extract	Apigenin, cirsimaritin, isothymusin and flavonoids	50%	10 days	Oral	↑ tissue formation; ↓ blood glucose level; ↑ hydroxyproline content; ↓ free radical's reduction; ↑ wound contraction; ↓ inflammatory marker	STZ-induced diabetic rats (45 mg/kg)	Gautam and Goel (2013)
109	*Prosopis farcta*	Fabaceae	Fruit	Aquatic Extract	Quercetin, Tryptamine, Apigenin 5- hydroxytryptamine and L-arabinose	Powder	15 days	Topical	↑ wound contraction; ↓ bacterial infection; ↓ antidiabetic activity; ↓ inflammation; ↑ tissue formation	STZ-induced diabetic rats (55 mg/kg)	Ranjbar-Heidari et al. (2012)
110	*Cymbopogon nardus*	Poaceae or Gramineae	Leaves	Hydro-distillated	Citral, 2,6-octadienal, 3,7-dimethyl, geranyl acetate, citronellal, geraniol, and citronellol	1 and 25 µg/day	21 days	Topical	↓ inflammatory cytokines; ↑ wound contraction; ↑ re-epithelialization; ↑ tissue formation; ↓ bacterial infection	STZ-induced diabetic mice (60 mg/kg)	Kandimalla et al. (2016)
111	*Cycas thouarsii*	Cycadaceae	Leaves	n-butanol fraction	Quercetin-3-glucuronide, naringenin, apigenin and genistein	2%	30 days	Topical	↓ MMP-9, chemokine; ↑ TGF- β1, EGF, caspase-9; ↑ wound contraction; ↓ bacterial infection; ↑ collagen synthesis	STZ-induced diabetic rats (65 mg/kg)	Binsuwaidan et al. (2022)

Table 3 (continued)

S. no	Plant name	Family	Part used	Extraction/ fraction	Active constituents	Doses of drugs	Duration of therapy	Drug administration	Molecular target and effect	Diabetes induction	Citation
112	*Juglans regia* L	Juglandaceae	Leaves	Methanolic extract	Flavonoids, phenolic acids and naphthoquinones	2 and 5%	21 days	Topical	↑ epidermis and dermis; ↑ fibroblasts proliferation; ↑ blood vessels; ↑ collagen deposition; ↑ TGF-β, VEGF levels; ↑ wound contraction; ↓ TNF-α, IL-1β levels	STZ-induced diabetic rats (55 mg/kg)	Nasiry et al. (2022)

CTGF, connective tissue growth factor; CAT, catalase; DNA, deoxyribonucleic acid; EGF, epidermal growth factor; FGF, fibroblast growth factor; GSH, glutathione; GLUT-1, glucose transporter-1; HIF-1α, hypoxia-inducible factor-1α; HIF, hypoxia-inducible factor; IL, interleukin; IGF, insulin-like growth factor; MDA, malondialdehyde; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; NO, nitric oxide; pDGF-β, platelet-derived growth factor-β; ROS, reactive oxygen species; SOD, superoxide dismutase; STZ, streptozotocin; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor; 11β HSD-1, 11β-hydroxysteroid dehydrogenase-1

area of research in this field is the use of green-synthesized nanoparticles for the treatment of diabetic wounds. In the case of diabetic wounds, green-synthesized nanoparticles have been shown to possess antimicrobial, antioxidant, and anti-inflammatory properties, which are essential for promoting wound healing. For instance, silver, gold, titanium dioxide ($TiO_{2)}$, copper, and zinc oxide nanoparticles synthesized using plant extracts have been shown to exhibit strong antimicrobial activity against a wide range of bacteria, including drug-resistant strains, which are commonly found in diabetic wounds (Ezhilarasu et al. 2020; Sharma et al. 2022). This makes them particularly attractive for wound-healing applications, as they can penetrate the skin and reach deep tissues, where they can release therapeutic agents and promote tissue regeneration (Qin et al. 2022). Green synthesis methods involve using natural sources, such as plant extracts, to reduce and stabilize the nanoparticles. This approach offers several advantages over conventional chemical synthesis methods, including improved biocompatibility, reduced toxicity, and cost-effectiveness (Hajialyani et al. 2018). In the context of diabetic wound healing, green-synthesized nanoparticles have been found to have anti-inflammatory, antioxidant, and antimicrobial properties, which can help to address the impaired wound healing process in diabetic individuals. Additionally, these nanoparticles can enhance angiogenesis and stimulate collagen production, which are essential for wound healing (Ezhilarasu et al. 2020). Ahmad et al. (2022) investigated the use of *Ocimum sanctum* leaf extract to synthesize TiO_2 nanoparticles for diabetic wound healing. The study found that the synthesized TiO_2 nanoparticles were spherical and polygonal in shape with sizes ranging from 75 to 123 nm. The developed TiO2 nanoparticles, when incorporated into 2% chitosan (CS) gel, exhibited desirable thixotropic properties with pseudo plastic behavior. In-vivo wound-healing studies and histopathological investigations of healed wounds demonstrated that the TiO_2 nanoparticles-containing CS gel had excellent wound-healing efficacy in diabetic rats. The study's findings highlight the potential of using green-synthesized TiO_2 nanoparticles-containing CS gel for diabetic wound healing (Ahmad et al. 2022).

Bai and Jarubula (2023) conducted a study on the synthesis of zinc oxide nanoparticles (ZnO NPs) using the leaf extract of the *Nigella sativa*. The researchers found that these ZnO NPs had the ability to restore levels of glycogen, insulin, and blood glucose, indicating their potential as a cost-effective and efficient treatment for diabetes and diabetic wounds. Moreover, the study suggested that ZnO NPs could be applied in the field of diabetic wound care during athletic training (Bai and Jarubula 2023). For SNPs, Mojally et al. (2022) conducted a study to assess the effectiveness of *Mentha piperita* and silver nanoparticle hydrogel films in treating wounds in diabetic rats. The researchers prepared

Table 4 Summarizes the naturally isolated compound responsible for the healing effects on DWs reported in the last 10 years (2013–2023)

S. no	Isolated compound	Medicinal plant	Doses of drugs	Duration of therapy	Diabetes induction	Wound model	Molecular target and effect	Citation
1	Quercetin	*Trifolium Alexandrinum*	100 mg/kg and 1%	20 days	STZ- induced diabetic rats (55 mg/kg)	2 cm × 2 cm (400 mm^2) full-thickness excision wound	↑ diabetic wound closure; ↑ tissue formation; ↑ collagen deposition; ↑ angiogenesis; ↓ inflammation; ↓ blood glucose	Ahmad et al. (2017)
			0.3%	19 days	STZ- induced diabetic rats (60 mg/kg)	(2 × 2 cm) full-thickness cutaneous wound	↑ IL-10, VEGF and TGF-β1; ↑ collagen deposition; ↑ wound closure; ↓ TNF-α, IL-1b, and MMP-9; ↑ angiogenesis; ↑ cytokines, growth factors	Kant et al. (2021)
2	Pongamol	*Tephrosia purpurea*	0.2 and 0.5% w/w	18 days	STZ- induced diabetic rats (50 mg/kg − 1)	Full-thickness excision wound	↑ hydroxyproline content; ↑ wound closure; ↑ angiogenesis; ↑ collagen deposition; ↓ inflammation; ↑ fibroblasts	Lodhi et al. (2013)
3	Neferine	*Nelumbo nucifera* (Lotus)	10 and 20%	14 days	STZ- induced diabetic rats (55 mg/kg)	(10 mm) full-thickness incisional wound cut	↑ re-epithelialization; ↑ wound closure; ↑ angiogenesis; ↑ collagen deposition; ↓ inflammation; ↓ blood glucose; ↑ macrophage (CD 68 and CD 163)	Li et al. (2020)
4	Plumbagin	*Plumbago indica*	10 and 20%	14 days	STZ- nicotinamide induced diabetic rats (55 mg/kg and 110 mg/kg)	(10 mm in diameter) full-thickness incisional wound cut	↓ ROS level; ↑ re-epithelialization; ↑ collagen deposition; ↓ inflammation; ↑ growth factors; ↑ angiogenesis; ↑ wound contraction	Shao et al. (2019)

Table 4 (continued)

S. no	Isolated compound	Medicinal plant	Doses of drugs	Duration of therapy	Diabetes induction	Wound model	Molecular target and effect	Citation
5	Luteolin	*Martynia annua*	0.2 and 0.5%w/w or 0.5 and 1% w/w	14 and 20 days	STZ- induced diabetic rats (45 and 50 mg/kg)	Full-thickness incision and excision wound	↑ wound contraction; ↑ angiogenesis; ↑ collagen deposition; ↑ fibroblasts; ↓ inflammation; ↑ re-epithelialization; ↓ ROS level	Lodhi and Singhai (2013), Ozay et al. (2018)
			100 mg/kg	14 days	STZ- induced diabetic rats (80 mg/kg)	(15×15 mm^2) incision wound on dorsal thorax	↑ re-epithelialization; ↓ inflammatory markers; ↑ collagen deposition; ↑ new blood vessels; ↓ MMPs level; ↓ ROS level	Chen et al. (2021)
6	Kirenol	*Siegesbeckia orientalis*	15 and 30%	14 days	STZ- induced diabetic rats (50 mg/kg)	Full-thickness excision wound	↓ inflammatory markers; ↓ MMPs level; ↑ angiogenesis; ↑ fibroblasts; ↑ new blood vessels; ↑ collagen deposition	Ren et al. (2020)
7	Kaempferol	–	0.5 and 1% w/w	14 days	STZ- induced diabetic rats (50 mg/kg)	(1.5 cm in diameter) excision wound and (4 cm long) incision wound	↑ hydroxyproline content; ↑ re-epithelialization; ↑ wound closure; ↑ collagen deposition; ↓ inflammatory markers; ↑ fibroblasts	Özay et al. (2019)
8	Arnebin-1	*Arnebia euchroma* (Zicao)	0.1%	7 days	Alloxan monohydrate induced diabetic rats (100 mg/kg)	(8 mm in diameter) full-thickness cutaneous wound	↑ cell migration; ↓ macrophages; ↑ fibroblasts; ↑ neovascularization; ↑ re-epithelialization; ↑ wound closure; ↓ inflammatory markers; ↑ VEGF promote wound healing	Zeng and Zhu (2014)

Table 4 (continued)

S. no	Isolated compound	Medicinal plant	Doses of drugs	Duration of therapy	Diabetes induction	Wound model	Molecular target and effect	Citation
9	20(S)-protopanaxadiol	*Panax notoginseng*	15 µl, 0.6, 6 and 60 mg/ ml^{-1}	14 days	db/db diabetic mice	Excisional wound splinting model	↑ wound closure; ↑ VEGF activates p70S6K through PI3K/Akt/mTOR and Raf/MEK/ERK signaling cascades; ↑ angiogenesis; ↑ collagen deposition; ↓ inflammatory markers	Zhang et al. (2017a)
10	Myricetin	–	3 µM	4 days	Fibroblasts from female T2DM patient	-	↑ MMPs level; ↓ MMP-1, MMP-2; ↑ wound closure; ↑ TIMP-1 level	Wu et al. (2016)
11	Rutin	–	100 mg/kg	21 days	STZ- induced diabetic rats (80 mg/kg)	(15×15 mm) incision wound	↑ body weight; ↑ metabolic dysfunctions; ↑ wound closure; ↓ inflammatory markers; ↑ angiogenesis; ↑ re-epithelialization	Chen et al. (2020)
12	Vicenin-2	–	12.5, 25, and 50 µM	14 days	STZ- induced diabetic rats (50 mg/kg)	(6 mm in diameter and 2 mm in depth) excision wound	↑ wound closure; ↓ pro-inflammatory cytokines; ↑ VEGF and TGF-β; ↓ nitric oxide; ↑ angiogenesis; ↑ collagen deposition	Tan et al. (2019)
13	Icariin	–	0.04, 0.2, 1, and 5 mg/µg	19 days	STZ- induced diabetic rats	(4 cm^2) full-thickness excision wound	↑ IL-10 level; ↑ wound closure; ↓ NF-κB and TNF-α; ↓ inflammatory markers; ↑ collagen deposition; ↑ angiogenesis	Singh et al. (2022)

Table 4 (continued)

S. no	Isolated compound	Medicinal plant	Doses of drugs	Duration of therapy	Diabetes induction	Wound model	Molecular target and effect	Citation
14	Mangiferin	*Mangifera indica*	1 and 2%	21 days	STZ- nicotinamide induced diabetic rats (65 mg/kg and 110 mg/kg)	Full-thickness excision wound	↑ wound closure; ↑ skin thickness; ↑ EGF, FGF, TGF-b, VEGF; ↑ PI3K, MMPs and Nrf2; ↓TNF-α and NF-kB p65; ↓ inflammatory markers; ↑ collagen deposition	Lwin et al. (2021)
15	Notoginsenoside R1		0.038 mg/cm^2	15 days	STZ-high-fat diet induced diabetic rats (35 mg/kg and 110 mg/kg)	(2 cm in diameter) full-thickness incision wound	↑ collagen deposition; ↑ platelet endothelial cells; ↑ wound closure; ↑ ECM, TIMP-1, FOS, TGF-β1; ↓ cleaved caspase-3; ↓ MMP-3, MMP-9,; ↓ IL-6, IL-1β level	Cao et al. (2022)
16	Ginsenoside Rb1	*Panax ginseng*	10 ng/mL	2 h	Human diabetic fibroblast	Patients with diabetic foot ulcers	↑ cell proliferation; ↑ collagen deposition; ↑ VEGF, TGF-β1; ↑ wound closure; ↓ inflammatory markers	Namgoong et al. (2019)
17	Patchouli alcohol	–	20 mg/kg and 0 ~ 30 mg/mL	7 days	High fat diet-fed mice	Full-thickness excision wound	↑ wound healing; ↓ inflammation; ↑ cell migration; ↑ AMPK or TGFb1	Kim et al. (2021)
18	Hsian-tsao	*Mesona procumbens Hemsl*	100 µL and 0 ~ 200 µg/mL	15 days	STZ- induced diabetic mice (65 mg/kg)	(8 mm) Two symmetrical wounds	↑ wound healing; ↑ IL-8, MIP-2, MCP-1; ↑ TIMP-1, VEGF; ↓ MMP-2, MMP-9,; ↓ ROS level; ↓ inflammatory markers	Fan et al. (2021)

Table 4 (continued)

S. no	Isolated compound	Medicinal plant	Doses of drugs	Duration of therapy	Diabetes induction	Wound model	Molecular target and effect	Citation
19	Berberine	*Coptis chinensis* Franch	0.06 mg/ml, 1.5625, 3.125, and 6.25 µM	12 days	STZ- high-fat diet induced diabetic rats	Full-thickness incision wound	↑ wound healing; ↑ ECM, GSH, SOD; ↓ ROS, MDA, caspase-3; ↑ MMP-9, TGF-β1; ↑ cell proliferation; ↑ collagen deposition; ↑ angiogenesis	Zhou et al. (2021b)
20	Syringic acid	–	2.5 and 5%	14 days	STZ- nicotinamide induced diabetic rats (55 mg/kg and 110 mg/kg)	(21 mm) full-thickness excision wound	↑ re-epithelialization; ↑ wound closure; ↑ hydroxyproline and protein; ↓ NF—κB p65, TNF -α,; ↓ IL-1β, IL-8 and IL-2; ↑ TGF-β1, Collagen-I; ↑ α-SMA and VEGF	Ren et al. (2019a)
21	Curcumin	*Curcuma longa* Linn	0.3%	19 days	STZ- induced diabetic rats (60 mg/kg)	(2×2 cm^2) full-thickness excision wound	↑ wound contraction; ↓ TNF-α, IL-1b, MMP-9; ↑ IL-10, VEGF, TGF-b1; ↑ HIF-1a, SDF-1α, HO-1; ↑ eNOS, SOD, GPx, GAP-43; ↑ collagen deposition	Kant et al. (2014)
			0.15%	19 days	STZ- induced diabetic rats (60 mg/kg)	(2×2 cm) full-thickness excision wound	↑ wound contraction; ↓ mRNA expressions; ↓ TNF-α, IL-1b, MMP-9; ↑ IL-10, VEGF, TGF-b1; ↑ HIF-1a, SDF-1α, HO-1; ↑ eNOS, SOD, GPx,; ↑ collagen deposition; ↑ fibroblast proliferation	Kant et al. (2017)

Table 4 (continued)

S. no	Isolated compound	Medicinal plant	Doses of drugs	Duration of therapy	Diabetes induction	Wound model	Molecular target and effect	Citation
22	d-limonene	–	50 mg/kg and 100 mg/kg	14 days	Alloxan induced diabetic mice	Full-thickness excision wound	↑ wound contraction; ↓ inflammatory markers; ↑ re-epithelialization; ↑ collagen deposition; ↑ tissue formation	Ahmad et al. (2014)
23	1,4-polyisoprene	*Sphenocentrum jollyanum* pierre	0.10% w/w	12 days	STZ- induced diabetic rats	Full-thickness excision wound	↑ wound contraction; ↑ collagen formation; ↓ inflammatory markers; ↑ hydroxyproline	Diovu et al. (2023)

AMPK, adenosine monophosphate activated protein kinase; AKT, protein kinase B; EGF, epidermal growth factor; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; FOS, fructo-oligosaccharides; GPx, glutathione peroxidase; GSH, glutathione; GAP-43, growth-associated protein-43; HO-1, heme oxygenase-1; IL, interleukin; MDA, malondialdehyde; MMPs, matrix metalloproteinase; mRNA, messenger ribonucleic acid; MIP-2, macrophage inflammatory protein-2; MCP-1, monocyte chemoattractant protein-1; NF-kB, nuclear factor kappa B; Nrf-2, nuclear-related factor-2; ROS, reactive oxygen species; SOD, superoxide dismutase; STZ, streptozotocin; SDF-1α, stromal cell-derived factor-1α; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor

the hydrogel films using a solvent- and diluent-free process that was environmentally friendly. Thirty rats were randomly assigned to one of five groups, and the results showed that Gel-I and fucidin groups had fully healed wounds after 22 days, whereas Gel-II groups healed by Day 16 (compared to Group 1st to day 25). Group-II diabetic rats took over 25 days to recover, but Gel-II improved wound healing. Both Gel-I and Gel-II also decreased fasting blood glucose levels, indicating that the *Mentha piperita* and SNPs effectively maintained their concentration at the wound site with low toxicity (Mojally et al. 2022). Furthermore, for the GNPs, Ponnanikajamideen et al. (2019) observed that administering gold nanoparticles to diabetic mice over a period of 21 days resulted in significant improvement in blood glucose, glycogen and insulin levels, and wound healing. These findings suggested that gold nanoparticles have the potential to be an effective treatment option for managing diabetes mellitus and reducing the size of wounds (Ponnanikajamideen et al. 2019). The green-synthesized nanoparticles have been found to promote wound healing by stimulating the migration of cells, re-epithelialization, angiogenesis, increase growth factors, reduced inflammation, collagen deposition, and new tissue formation. Table 5 provides a summary of recent *in-vitro and in-vivo* studies that have investigated the diabetic wound-healing properties of various green-synthesized nanoparticles.

Human (clinical trial) in-vivo-based studies A common and serious complication of diabetes is the development of diabetic wounds, especially in the lower limbs, which can be challenging to heal and may result in severe infections and amputations. Indian traditional medicines have utilized natural products for wound care for a long time, and many of these products possess properties, such as antimicrobial, anti-inflammatory, and antioxidant that could potentially aid in the treatment of diabetic wounds (Bandyk 2018). Several human-based studies have investigated the use of natural products in the treatment of diabetic wounds. These studies have generally focused on topical applications of natural products, such as creams, ointments, and dressings (Sharma et al. 2021a; Herman and Herman 2023). Some of the most promising natural products studied in this context include, study conducted by Najafian et al. (2018), who found that the use of *Plantavera* gel significantly reduced the total ulcer score and ulcer surface in patients with diabetic wounds compared to the control group, without causing any side effects. However, no significant difference was observed in terms of ulcer depth between the two groups (Najafian et al. 2018). In addition, Tonaco et al. (2018) analyzed the results of intention-to-treat analysis on patients with ulcers in the control and P1G10 groups. The P1G10 group was found to be 2.95-fold more effective in achieving 100% healing and 2.52-fold more effective in achieving 80% healing com-

Table 5 Summarizes the green-synthesized nanoparticle responsible for the healing effects on DWs reported in the last 8 years (2016–2023)

S. no	Plant name and family	Family	Type of NPs	Methodology	Characterizations	Doses of drugs	Duration of therapy	*In-vitro/in-vivo* wound model diabetes induction	Effect	Citation
1	*Chamaecostus Cuspidatus*	Costaceae	Gold	Green synthesis of GNPs	UV spectroscopy, XRD, SEM, TEM and TGA	1.5 mg/kg	21 days	*In-vivo* Excision STZ	GNPs showing significantly higher wound recovery showed	Ponnanikajamideen et al. (2019)
2	*Mentha piperita*	Lamiaceae	Silver	Biosynthesis SNPs	–	–	25 days	*In-vivo* Excision STZ	SNPs hydrogel film significantly improved wound-healing time in diabetic	Mojally et al. (2022)
3	*Scutellaria barbata*	Lamiaceae	Silver	Green synthesis of SNPs	UV spectroscopy, TEM, XRD, FTIR and atomic force microscopy	5 and 7.5 mg	24 h	*In-vitro* Wound scratch *L929* fibroblast	SNPs showing potent diabetic wound healing property	Veeraraghavan et al. (2021)
4	*Malva sylvestris*	Malvaceae	NP_S fibers	Biosynthesis by electrospinning	Swelling ratio, release behavior, FTIR and water vapor transmission rate	15 and 20% w/w	14 days	*In-vitro* and *In-vivo* Excision STZ	NP_S fibers significantly improve the inflammation, and diabetic wound healing potential	Almasian et al. (2020)
5	*Aloe vera*	Asphodelaceae	NP_S emulsion	Insulin loaded nanoemulsion	Physical stability and pH, particle size and zeta potential, drug content, Spreadability and viscosity	2.5 g/kg and 0.1 IU	15 days	*In-vivo* Incision Alloxan	NP_S emulsion application improved the wound healing, while various phytoconstituents in *Aloe vera* also significantly contributed to the overall therapy	Chakraborty et al. (2021)

Table 5 (continued)

S. no	Plant name and family	Family	Type of NPs	Methodology	Characterizations	Doses of drugs	Duration of therapy	*In-vitro/in-vivo* wound model diabetes induction	Effect	Citation
6	*Archidendron pauciflorum*	Fabaceae	PLGA NP_S	Green synthesis PLGA NP_S	–	2.5, 5 and 10%	14 days	*In-vivo* Incision STZ	PLGA NP_S ointment most effective in accelerating wound healing in the skin of diabetic mice	Malini et al. (2020)
7	*Mikania micrantha*	Asteraceae	Nanogel	Green synthesis of emulsification diffusion method	Physical parameters, homogeneity, pH, and size	–	14 days	*In-vivo* Excision Alloxan	*M. micrantha* nanogels have the potential as a treatment for diabetic wound healing	Sumantri et al. (2021)
8	*Aerva lanata*	Amaranthaceae	Silver	Phyto- fabricated SNPs	–	5, 10 and 20 µg/mL	24 h	*In-vitro* *Pseudomonas aeruginosa* Culture of DFU	*A. lanata* have the potential as a treatment for diabetic foot ulcer derived resistant bacterial isolates	Thanganadar Appapalam et al. (2020)
9	*Aristolochia indica*	Aristolochiaceae	Zinc oxide	Green-synthesized ZnO NPs	UV spectroscopy and FTIR	0.01 ml	24 h	*In-vitro* *E. coli* Pus culture of DFU	ZnO NPs exhibited strong bactericidal properties against clinically isolated Multidrug resistant strains isolated from diabetic Foot Ulcer	Steffy et al. (2018)
10	*Azadirachta indica*	Meliaceae	Silver	Biosynthesis SNPs	UV spectroscopy, XRD and SEM	2.5 + 3.2 mg and 5 + 3.2 mg	15 days	*In-vivo* Thermal wound STZ	SNPs showing potent diabetic wound healing property	Bhagavathy and Kancharla (2016)

Table 5 (continued)

S. no	Plant name and family	Family	Type of NPs	Methodology	Characterizations	Doses of drugs	Duration of therapy	*In-vitro/in-vivo* wound model diabetes induction	Effect	Citation
11	*Pomegranate*	Punicaceae	Silver	Green synthesis of SNPs	–	5.55 µg/mL	14 days	*In-vivo* Excision STZ	SNPs promoting significant improvement in terms of healing and wound closure	Scappaticci et al. (2021)
12	*Melia azedarach*	Meliaceae	Silver	Biosynthesis SNPs	UV spectroscopy, SEM, TEM, XRD, energy dispersive spectroscopy and FTIR	1000 µg/mL	24 h	*In-vitro* Wound scratch Fibroblast cells	Scratch assay proved SNPs have higher potential in diabetic wound healing	Chinnasamy et al. (2019)
13	*Aloe arborescens*	*Asphodelaceae*	Silver	Green synthesis of SNPs	–	830 nm with 5 J/cm^2	48 h	*In-vitro* Wound scratch Fibroblast cells	SNPs demonstrated promising results to achieve progressive migration and diabetic wound closure	Kumar et al. (2020)
14	*Lepidium sativum*	Brassicaceae	3D nano-oleogel	Green synthesis of nano-oleogel	GC/MS and TEM	100 mg	5 days	*In-vitro* and *In-vivo* Excision Alloxan	3D nano-oleogel showed a significant reduction of wound diameter, a significant decline of TNF-α and MMP-9 level in skin homogenate, in addition to a significant elevation of VEGF level	Kamel et al. (2021)
15	*Turbinaria conoides*	Sargassaceae	Silver	Biosynthesis SNPs	SEM, XRD, FTIR and Energy dispersive X-ray analysis	5 µl; 1×10^8 CFU/ml	16–20 h	*In-vitro* - Diabetic foot ulcer	*T. conoides* established their utility against bacteria from diabetic wound	Suresh et al. (2021)

Table 5 (continued)

S. no	Plant name and family	Family	Type of NPs	Methodology	Characterizations	Doses of drugs	Duration of therapy	*In-vitro/in-vivo* wound model diabetes induction	Effect	Citation
16	*Pterocarpus marsupium*	Fabaceae	Chitosan	Green synthesis of chitosan-loaded nanoparticles	SEM and particle size	0.4, 0.8, and 1.2% w/v	18 days	*In-vivo* Excision STZ	*P. marsupium* indicate the effectiveness of optimized nanocomposites as a potential treatment for curing diabetic wounds	Manne et al. (2021)
17	*Syzygium cumini*	Myrtaceae	Silver	Green Synthesis of SNP_S	UV spectroscopy, Energy dispersive X-ray spectroscopy, TEM, zeta potential, FTIR and XRD	1,5 ans 10 mM	18 days	*In-vivo* Excision STZ	SNP_S application on acute and diabetic wounds of mice documented enhanced tissue repair (99% wound closure) via decrease in inflammation; increase in angiogenesis, collagen deposition	Singla et al. (2017a)
18	*Dendrocalamus hamiltonii* and *Bambusa bambos*	Poaceae	Silver	Green Synthesis of SNP_S	–	–	18 days	*In-vivo* Excision STZ	*Bambusa* indicate the effectiveness of optimized nanocomposites as a potential treatment for curing diabetic wounds	Singla et al. (2017b)

Table 5 (continued)

S. no	Plant name and family	Family	Type of NPs	Methodology	Characterizations	Doses of drugs	Duration of therapy	*In-vitro/in-vivo* wound model diabetes induction	Effect	Citation
19	*Ocimum sanctum*	Lamiaceae	Titanium Dioxide	Green Synthesis of TiO_2 NPs	FTIR, XRD, SEM, TEM DLS analysis	1% w/w, 2% w/v and 20 mg/kg	21 days	*In-Vitro* Excision STZ	TiO_2 nanoparticles-containing chitosan (CS) gel, along with *Ocimum sanctum*, was effective in healing wounds in diabetic rats	Ahmad et al. (2022)
20	*Nigella sativa*	Ranunculaceae	Zinc Oxide	Green Synthesis of ZnO NPs	FESEM, EDS, UV–Vis, FTIR and XRD	-	21 days	*In-vivo* Excision STZ	ZnO NPs showing potent diabetic wound healing property	Bai and Jarubula (2023)

FTIR, fourier transform infrared; GNPs, gold nanoparticle; GC/MS, gas chromatography–mass spectrometer; MMP-9, matrix metallopeptidase-9; NP_S, nanoparticle; PLGA NP_S, co-polymer poly (lactic-co-glycolic acid) nanoparticle; STZ, streptozotocin; SNPs, silver nanoparticle; SEM, scanning electron microscope; TiO_2, titanium dioxide; TiO_2 NPs, titanium dioxide nanoparticle; TNF-α, tumor necrosis factor-α; TGA, thermogravimetric analysis; TEM, transmission electron; UV spectroscopy, ultra-visible spectroscopy microscope; VEGF, vascular endothelial growth factor; XRD, X-ray diffraction; ZnO NPs, zinc oxide nanoparticle

Table 6 List of clinical trial natural products responsible for the healing effects on DWs

S. no	Drug	Study design	Doses of drugs	Duration of therapy	Application	Effect	Citation
1	*Aloe vera*	Randomized Double-blind clinical trial	–	4 weeks	Applied topically	The wound size was decreased and the healing time was reduced	Najafian et al. (2018)
		Randomized clinical trial	–	15 days	*Aloe vera* ointment	Accelerated diabetic wound healing	Babaei et al. (2018)
2	*Vasconcellea cundinamarcensis* (P1G10)	Double-blind randomized pilot trail	0.1%	16 weeks	Topical dressing	The study showed that the (P1G10) group was significantly more effective in achieving complete and partial ulcer healing compared to the control group	Tonaco et al. (2018)
3	*Actindia deliciosa* (kiwifruit)	Randomized clinical trial	500 and 600 mg	21 days	Extract drug twice in a day	Kiwifruit treatment resulted in significant improvements in surface area reduction, collagen and granulation tissue formation, and angiogenesis in foot ulcers. However, no significant antibacterial effect was observed	Mohajeri et al. (2014)
4	*Plectranthus amboinicus and Centella asiatica*	Randomized controlled clinical trail	1.25%	14 days	Topical cream dressing	*P. amboinicus* and *C. asiatica* is a safe and effective alternative to hydrocolloid fiber dressing for treating DWs	Kuo et al. (2012)
5	*Ageratina pichinchensis*	Randomized, controlled pilot study	1 and 5%	6 weeks	Topical cream dressing	*Ageratina pichinchensis* accelerated diabetic wound healing	Romero-Cerecero et al. (2015)
6	Birch bark and Sunflower oil	Randomized phase III Clinical Trials	10 and 90%	21 days	Topical betulin gel	This product speeds up the process of re-epithelialization in wounds that are partially thick	Barret et al. (2017)
7	Royal jelly	Double-blind placebo-controlled clinical trial	5%	38 days	Topical royal jelly	Healing area, healing rate, and time not showing any change with placebo treated group	Siavash et al. (2015)
8	Olive oil	Randomized, Double-blind Clinical trial	0.9%	4 weeks	Topical Olive oil	Olive oil can lead to significant improvements in ulcer area, depth, and healing, without any adverse effects	Nasiri et al. (2015)

Table 6 (continued)

S. no	Drug	Study design	Doses of drugs	Duration of therapy	Application	Effect	Citation
9	*Manuka* honey	Randomized Clinical trials	–	6 weeks	Manuka honey-impregnated dressing	The treated group exhibited a substantial decrease in healing time compared to the control group. However, there was no significant difference in the percentage of healed ulcers between the two groups	Kamaratos et al. (2014)
10	*Securinega leucopyrus* (Katupila)	Case Study	500 mg	30 days	Topical paste apply once daily	The local application of *Securinega leucopyrus* in paste form once daily may have a beneficial effect in promoting the healing of DWs	Dudhamal et al. (2014)
11	*Azadirachta indica*	Randomized clinical trials	–	30 days	Extract irrigation	*Azadirachta indica* leaf extract irrigation was found to significantly improve wound healing and related variables in foot ulcers without causing any systematic complications	Jayalakshmi et al. (2021)
12	*Plantago major*	Randomized open-label controlled clinical trial	10%	14 days	Topical gel dressing	*Plantago* extract gel significantly reduces wound size and increases the rate of complete wound healing compared to the control group	Ghanadian et al. (2022)

pared to the control group (Tonaco et al. 2018). The study by Jayalakshmi et al. (2021), found that the neem leaves extract showed significant improvement in wound-healing score (PUSH score) and other wound variables compared to the control group ($p < 0.001$) (Jayalakshmi et al. 2021). Moreover, Ghanadian et al. (2022) showed that *Plantago* extract gel was significantly more effective than the control group in reducing wound size after the first and second week of treatment ($p < 0.001$). Moreover, the drug group had a significantly higher number of patients with complete wound healing compared to the control group (OR: 3.129, 95% CI: 1.685–5.809, $p < 0.001$) (Ghanadian et al. 2022). These products have been shown to improve wound healing and reduce the risk of infection in patients with diabetic wounds. While the exact mechanisms underlying the therapeutic effects of natural products in diabetic wound healing are not fully understood, it is thought that their antimicrobial, anti-inflammatory, and antioxidant properties may play important roles. Additionally, some natural products may stimulate the growth and differentiation of cells involved in wound healing, such as fibroblasts and keratinocytes. The natural products have been found to promote wound healing by stimulating the migration of cells, re-epithelialization, angiogenesis, increase growth factors, reduced inflammation, collagen deposition, and new tissue formation. Table 6 provides a summary of recent clinical trial studies that have investigated the diabetic wound-healing properties of various natural products.

Future therapeutic strategies

Diabetes, peripheral neuropathy, peripheral vascular disease, and foot conditions are all risk factors for DWs. However, despite the widespread adoption of standard care for DWs and the development of technologies such as bioengineered skin cells, diabetic patients continue to experience a less than 50% rate of wound healing. Natural product-based treatments for DWs have been used for centuries in traditional medicine, and recent research has shown their potential as a complementary therapy for diabetic patients. Several plants, including *aloe vera*, *Curcuma longa*, *Neem*, and *Annona squamosa*, have been studied for their diabetic wound-healing properties. Natural products are bioactive compounds that have been shown to have anti-inflammatory, antioxidant, and antibacterial effects, making them promising candidates for treating DWs. In addition to traditional plant-based treatments, advances in biotechnology have led to the development of plant-based wound dressings. These are made from natural materials, such as chitosan, collagen, and alginate, and have been shown to promote wound healing and reduce the risk of infection. Nevertheless, non-traditional therapeutic approaches, including single and dual growth factors, skin substitutes, cytokine stimulators and inhibitors, matrix metalloproteinase inhibitors, gene and stem cell therapy, extracellular matrix, and angiogenesis stimulators, are rapidly advancing DWs research. Recombinant growth factors, platelet-rich plasma, sphingosine 1-phosphate, stem cell therapy, matrix metalloproteinase inhibitors, shock-wave therapy, laser therapy, and natural products are among the emerging therapeutic strategies for DWs. Laser therapy, in particular, shows promise as a future therapeutic option. These techniques are essential for developing more convenient, safe, and effective therapies for DWs. Despite being mostly experimental, these techniques have shown great potential in clinical trial. However, most of these methods are still in the early stages of development.

Conclusion

Diabetes is a prevalent cause of impaired wound healing, which can have devastating consequences for patients. Over the past few years, there has been a surge of research in the field of DWs' treatment. Many studies have pointed out several factors that contribute to slow healing in diabetic patients. Fortunately, there has been significant progress in developing novel treatment techniques and products for wound healing in diabetics. One promising avenue for treatment is the use of natural products and their bioactive constituents. These can be used either as a supplement to standard therapy or as an alternative to synthetic drugs, as they offer a wide range of potential therapeutic benefits. These benefits include antimicrobial, anti-inflammatory, antioxidant, angiogenic, keratinocyte and cytokine stimulation, and growth factor modulation, which can promote fibroblast migration and proliferation. While several approaches, such as growth factors and other cytokine modulators, anti-inflammatory medications, MMP inhibitors, angiogenesis stimulators, and ECM stimulators, have been tested, none have shown significant success. However, recent research has shown that combinational techniques have outperformed the traditional approaches, which has given researchers optimism for creating innovative carriers while also understanding the fundamental methodology. Looking ahead, future research in the treatment of diabetic wounds could benefit from a combination of treatments, resulting in faster healing. Researchers should continue to identify different substances that can aid wound healing at various stages in diabetic patients. As healing progresses, improved clinical methods and systems may help reveal the full extent of healing. Overall, with continued research and development, there is hope for finding better treatment and improving the quality of life for patients suffering from diabetic wounds.

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Declarations

Conflict of interest The authors declare no competing interest.

References

Abdullah FI, Chua LS, Mohd Bohari SP, Sari E (2020) Rationale of *Orthosiphon aristatus* for healing diabetic foot ulcer. Nat Prod Commun. https://doi.org/10.1177/1934578X20953308

Abedin-Do A, Zhang Z, Douville Y et al (2021) Effect of electrical stimulation on diabetic human skin fibroblast growth and the secretion of cytokines and growth factors involved in wound healing. Biology (basel) 10:1–14. https://doi.org/10.3390/biology10070641

Achar RAN, Silva TC, Achar E et al (2014) Use of insulin-like growth factor in the healing of open wounds in diabetic and non-diabetic rats. Acta Cir Bras 29:125–131. https://doi.org/10.1590/S0102-86502014000200009

Adeleke O, Oboh G, Adefegha S, Osesusi A (2022) Effect of aqueous extract from root and leaf of *Sphenocentrum jollyanum* pierre on wounds of diabetic rats: influence on wound tissue cytokines, vascular endothelial growth factor and microbes. J Ethnopharmacol 293:1–8. https://doi.org/10.1016/j.jep.2022.115266

Agyare C, Akindele AJ, Steenkamp V (2019) Natural products and / or isolated compounds on wound healing. Evid-Based Complement Altern Med. https://doi.org/10.1155/2019/4594965

Ahluwalia R, Maffulli N, Lázaro-Martínez JL et al (2021) Diabetic foot off loading and ulcer remission: exploring surgical off-loading. Surgeon 19:e526–e535. https://doi.org/10.1016/j.surge.2021.01.005

Ahmad M, Khan TH, Ansari MN, Ahmad SF (2014) Enhanced wound healing by topical administration of d-limonene in alloxan induced diabetic mice through reduction of pro-inflammatory markers and chemokine expression. BMC Genomics 15:1–2. https://doi.org/10.1186/1471-2164-15-s2-p29

Ahmad M et al (2017) Hypoglycemic, hypolipidemic, and wound healing potential of quercetin in streptozotocin-induced diabetic rats. Pharmacogn Mag 13(Suppl):179–188. https://doi.org/10.4103/pm.pm

Ahmad MZ, Alasiri AS, Ahmad J et al (2022) Green synthesis of titanium dioxide nanoparticles using *Ocimum sanctum* leaf extract. In vitro characterization and its healing efficacy in diabetic wounds. Molecules 27:1–17. https://doi.org/10.3390/molecules27227712

Ahmadian R, Bahramsoltani R, Marques AM et al (2021) Medicinal plants as efficacious agents for diabetic foot ulcers: a systematic review of clinical studies. Wounds 33:207–218. https://doi.org/10.25270/wnds/2021.207218

Ahmed M, Reffat SA, Hassan A, Eskander F (2017) Platelet-rich plasma for the treatment of clean diabetic foot ulcers. Ann Vasc Surg 38:206–211. https://doi.org/10.1016/j.avsg.2016.04.023

Ajani RS, Olateju OJ (2020) Mangifera indica (Mango) bark therapy potentiates wound healing in diabetic rats. J Complement Altern Med Res 10:1–13. https://doi.org/10.9734/jocamr/2020/v10i130152

Aksoy H, Sen A, Sancar M et al (2016) Ethanol extract of *Cotinus coggygria* leaves accelerates wound healing process in diabetic rats. Pharm Biol 54:2732–2736. https://doi.org/10.1080/13880209.2016.1181660

Al Sarayreh A, Oran SA, Shakhanbeh JM et al (2022) Effects of the oral administration of methanolic extracts of some Jordanian medicinal plants on wound healing in diabetic rats. SSRN Electron J 8:e10071. https://doi.org/10.2139/ssrn.4077007

Alavi A, Sibbald RG, Mayer D et al (2014) Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol 70:1.e1-1.e18. https://doi.org/10.1016/j.jaad.2013.06.055

Alexiadou K, Doupis J (2012) Management of diabetic foot ulcers. Diabetes Ther 3:1–15. https://doi.org/10.1007/s13300-012-0004-9

Al-Ghanayem AA, Alhussaini MS, Asad M, Joseph B (2022) *Moringa oleifera* leaf extract promotes healing of infected wounds in diabetic rats: evidence of antimicrobial, antioxidant and proliferative properties. Pharmaceuticals. https://doi.org/10.3390/ph15050528

Ali S, Ishteyaque S, Khan F et al (2021) Accelerative wound-healing effect of aqueous *Anthocephalus cadamba* leaf extract in a diabetic rat model. Int J Low Extrem Wounds. https://doi.org/10.1177/15347346211018330

Ali R, Khamis T, Enan G et al (2022) The healing capability of clove flower extract (CFE) in streptozotocin-induced (STZ-induced) diabetic rat wounds infected with multidrug resistant bacteria. Molecules. https://doi.org/10.3390/molecules27072270

Almasian A, Najafi F, Eftekhari M et al (2020) Polyurethane/carboxymethylcellulose nanofibers containing *Malva sylvestris* extract for healing diabetic wounds: Preparation, characterization, in vitro and in vivo studies. Mater Sci Eng C. https://doi.org/10.1016/j.msec.2020.111039

Almeida PMD, Mandal T, Laxminarayana Bairy K, Adiga S (2017) Effect of oil extract of *Jasminum grandiflorum* leaves on wound healing activity in albino rats. Adv Sci Lett 23:1957–1959. https://doi.org/10.1166/asl.2017.8501

Alsaimary IEA (2010) Bacterial wound infections in diabetic patients and their therapeutic implications. Internet J Microbiol 7:12–15

Alsarayreh AZ, Oran SA, Shakhanbeh JM (2021) Effect of *Rhus coriaria* L. methanolic fruit extract on wound healing in diabetic and non-diabetic rats. J Cosmet Dermatol 42:733–738. https://doi.org/10.1111/jocd.14668

Alsarayreh AZ, Attalah Oran S, Shakhanbeh JM (2022) In vitro and in vivo wound healing activities of *Globularia arabica* leaf methanolic extract in diabetic rats. J Cosmet Dermatol 42:733–738. https://doi.org/10.1111/jocd.14882

Altıparmak M, Eskitaşçıoğlu T (2018) Comparison of systemic and topical *Hypericum perforatum* on diabetic surgical wounds. J Investig Surg 31:29–37. https://doi.org/10.1080/08941939.2016.1272654

Amirah N, Zaid M, Gan SH et al (2022) Promising natural products in new drug design, development, and therapy for skin disorders : an overview of scientific evidence and understanding their mechanism of action. Drug Des Dev Ther 6:23–66

Andjić M, Božin B, Draginić N et al (2021) Formulation and evaluation of *Helichrysum italicum* essential oil-based topical formulations for wound healing in diabetic rats. Pharmaceuticals. https://doi.org/10.3390/ph14080813

Andjić M, Draginić N, Kočović A et al (2022) Immortelle essential oil-based ointment improves wound healing in a diabetic rat model. Biomed Pharmacother. https://doi.org/10.1016/j.biopha.2022.112941

Angelo LS, Kurzrock R (2007) Vascular endothelial growth factor and its relationship to inflammatory mediators. Clin Cancer Res 13:2825–2830. https://doi.org/10.1158/1078-0432.CCR-06-2416

Ansari P, Akther S, Hannan JMA et al (2022a) Pharmacologically active phytomolecules isolated from traditional antidiabetic plants and their therapeutic role for the management of diabetes mellitus. Molecules. https://doi.org/10.3390/molecules27134278

Ansari P, Akther S, Khan JT et al (2022b) Hyperglycaemia-linked diabetic foot complications and their management using conventional and alternative therapies. Appl Sci. https://doi.org/10.3390/app122211777

Armstrong DG, Hanft JR, Driver VR et al (2014) Effect of oral nutritional supplementation on wound healing in diabetic foot ulcers: a prospective randomized controlled trial. Diabet Med 31:1069–1077. https://doi.org/10.1111/dme.12509

Arumugam G, Manjula P, Paari N (2013) A review: anti diabetic medicinal plants used for diabetes mellitus. J Acute Dis 2:196–200. https://doi.org/10.1016/S2221-6189(13)60126-2

Asif M, Zafar M, Saleem M et al (2022) Evaluation of antidiabetic and wound healing properties of ethanol extract of *Hedera nepalensis* in alloxan-induced diabetic rats. S Afr J Bot 146:118–126. https://doi.org/10.1016/j.sajb.2021.10.007

Augustine R, Hasan A, Dalvi YB et al (2021) Growth factor loaded in situ photocrosslinkable poly(3-hydroxybutyrate-co-3-hydroxyvalerate)/gelatin methacryloyl hybrid patch for diabetic wound healing. Mater Sci Eng C 118:111519. https://doi.org/10.1016/j.msec.2020.111519

Avishai E, Yeghiazaryan K, Golubnitschaja O (2017) Impaired wound healing: facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine. EPMA J 8:23–33. https://doi.org/10.1007/s13167-017-0081-y

Babaei S, Bayat M, Nouruzian M, Bayat M (2013) Pentoxifylline improves cutaneous wound healing in streptozotocin-induced diabetic rats. Eur J Pharmacol 700:165–172. https://doi.org/10.1016/j.ejphar.2012.11.024

Babaei V, Afradi H, Gohardani HZ et al (2017) Management of chronic diabetic foot ulcers using platelet-rich plasma. J Wound Care 26:784–787. https://doi.org/10.12968/jowc.2017.26.12.784

Babaei K, Nejatii S, Najafi B et al (2018) Studying the effect of Aloe vera ointment on wound healing of CABG surgery in diabetic patients. J Res Med Dent Sci 6:256–260. https://doi.org/10.24896/jrmds.20186141

Bahado-Singh PS (2014) Wound healing potential of *Tillandsia recurvata* and *Guaiacum officinale* in streptozotocin induced type 1 diabetic rats. Am J Biomed Life Sci 2:146. https://doi.org/10.11648/j.ajbls.20140206.12

Bai X, Jarubula R (2023) Development of novel green synthesized Zinc oxide nanoparticles with antibacterial activity and effect on diabetic wound healing process of excisional skin wounds in nursing care during sports training. Inorg Chem Commun 150:4–6. https://doi.org/10.1016/j.inoche.2023.110453

Bain MA, Koullias GJ, Morse K et al (2020) Type i collagen matrix plus polyhexamethylene biguanide antimicrobial for the treatment of cutaneous wounds. J Comp Eff Res 9:691–703. https://doi.org/10.2217/cer-2020-0058

Baiula M, Greco R, Ferrazzano L et al (2020) Integrin-mediated adhesive properties of neutrophils are reduced by hyperbaric oxygen therapy in patients with chronic non-healing wound. PLoS ONE 15:1–22. https://doi.org/10.1371/journal.pone.0237746

Bandyk DF (2018) The diabetic foot: pathophysiology, evaluation, and treatment. Semin Vasc Surg 31:43–48. https://doi.org/10.1053/j.semvascsurg.2019.02.001

Bardaa S, Makni K, Boudaouara O et al (2021) Development and evaluation of the wound healing effect of a novel topical cream formula based on Ginkgo biloba extract on wounds in diabetic rats. Biomed Res Int. https://doi.org/10.1155/2021/6474706

Barret JP, Podmelle F, Lipový B et al (2017) Accelerated re-epithelialization of partial-thickness skin wounds by a topical betulin gel: results of a randomized phase III clinical trials program. Burns 43:1284–1294. https://doi.org/10.1016/j.burns.2017.03.005

Barrientos S, Stojadinovic O, Golinko MS et al (2008) Growth factors and cytokines in wound healing. Wound Repair Regen 16:585–601. https://doi.org/10.1111/j.1524-475X.2008.00410.x

Barua CC, Begum SA, Pathak DC, Bora RS (2013) Wound healing activity of *Alternanthera brasiliana* kuntze and its anti oxidant profiles in experimentally induced diabetic rats. J Appl Pharm Sci 3:161–166. https://doi.org/10.7324/JAPS.2013.31029

Basiri R, Spicer MT, Levenson CW et al (2020) Nutritional supplementation concurrent with nutrition education accelerates the wound healing process in patients with diabetic foot ulcers. Biomedicines 8:1–14. https://doi.org/10.3390/BIOMEDICINES8080263

Basiri R, Spicer M, Levenson C et al (2022) Improving dietary intake of essential nutrients can ameliorate inflammation in patients with diabetic foot ulcers. Nutrients. https://doi.org/10.3390/nu14122393

Basu Mallik S, Jayashree BS, Shenoy RR (2018) Epigenetic modulation of macrophage polarization- perspectives in diabetic wounds. J Diabetes Complicat 32:524–530. https://doi.org/10.1016/j.jdiacomp.2018.01.015

Bechara N, Flood VM, Gunton JE (2022) A systematic review on the role of vitamin C in tissue healing. Antioxidants 11:1–12. https://doi.org/10.3390/antiox11081605

Beer HD, Longaker MT, Werner S (1997) Reduced expression of PDGF and PDGF receptors during impaired wound healing. J Invest Dermatol 109:132–138

Bekele F, Chelkeba L (2020) Amputation rate of diabetic foot ulcer and associated factors in diabetes mellitus patients admitted to Nekemte referral hospital, western Ethiopia: prospective observational study. J Foot Ankle Res 13:1–8. https://doi.org/10.1186/s13047-020-00433-9

Bellingeri A, Falciani F, Traspedini P et al (2016) Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. J Wound Care 25:160–168. https://doi.org/10.12968/jowc.2016.25.3.160

Bettahi I, Sun H, Gao N et al (2014) Genome-wide transcriptional analysis of differentially expressed genes in diabetic, healing corneal epithelial cells: hyperglycemia-suppressed TGFB3 expression contributes to the delay of epithelial wound healing in diabetic corneas. Diabetes 63:715–727. https://doi.org/10.2337/db13-1260

Bhagavathy S, Kancharla S (2016) Wound healing and angiogenesis of silver nanoparticle from *Azadirachta indica* in diabetes induced mice. Int J Herb Med 4:24–29

Bhattacharya S, Aggarwal R, Singh VP et al (2015) Downregulation of miRNAs during delayed wound healing in diabetes: role of dicer. Mol Med 21:847–860. https://doi.org/10.2119/molmed.2014.00186

Bhora FY, Dunkin BJ, Batzri S et al (1995) Effect of growth factors on cell proliferation and epithelialization in human skin. J Surg Res 59:236–244

Binsuwaidan R, Elekhnawy E, Elseady WS et al (2022) Antibacterial activity and wound healing potential of *Cycas thouarsii* R.Br n-butanol fraction in diabetic rats supported with phytochemical profiling. Biomed Pharmacother 155:113763. https://doi.org/10.1016/j.biopha.2022.113763

Biswas S, Roy S, Banerjee J et al (2010) Hypoxia inducible microRNA 210 attenuates keratinocyte proliferation and impairs closure in a murine model of ischemic wounds. Proc Natl Acad Sci U S A 107:6976–6981. https://doi.org/10.1073/pnas.1001653107

Bitar MS, Labbad ZN (1996) Transforming growth factor-β and insulin-like growth factor-I in relation to diabetes-induced impairment of wound healing. J Surg Res 61:113–119. https://doi.org/10.1006/jsre.1996.0090

Bramara BV, Vasavi HS, Sudeep HV, Shyam Prasad K (2017) Hydroalcoholic extract from *Lepidium meyenii* (Black Maca) root exerts wound healing activity in Streptozotocin-induced diabetic rats. Wound Med 19:75–81. https://doi.org/10.1016/j.wndm.2017.10.003

Brem H, Tomic-canic M (2007) Cellular and molecular basis of wound healing in diabetes find the latest version: cellular and molecular basis of wound healing in diabetes. J Clin Investig 117:1219–1222. https://doi.org/10.1172/JCI32169.Despite

Brocco E, Ninkovic S, Marin M et al (2018) Diabetic foot management: multidisciplinary approach for advanced lesion rescue. J Cardiovasc Surg (torino) 59:670–684. https://doi.org/10.23736/S0021-9509.18.10606-9

Brown DL, Kane CD, Chernausek SD, Greenhalgh DG (1997) Differential expression and localization of insulin-like growth factors I and II in cutaneous wounds of diabetic and nondiabetic mice. Am J Pathol 151:715–724

Bruhn-Olszewska B, Korzon-Burakowska A, Gabig-Cimińska M et al (2012) Molecular factors involved in the development of diabetic foot syndrome. Acta Biochim Pol 59:507–513. https://doi.org/10.18388/abp.2012_2085

Brunner LM, He Y, Cousin N et al (2023) Promotion of Lymphangiogenesis by targeted delivery of VEGF-C improves diabetic wound healing. Cells. https://doi.org/10.3390/cells12030472

Burgess JL, Wyant WA, Abujamra BA et al (2021) Diabetic wound-healing science

Burstein NL (1987) Growth factor effects on corneal wound healing. J Ocul Pharmacol 3:263–277. https://doi.org/10.1089/jop.1987.3.263

Bus SA (2016) The role of pressure offloading on diabetic foot ulcer healing and prevention of recurrence. Plast Reconstr Surg 138:179S-187S. https://doi.org/10.1097/PRS.0000000000002686

Cam ME, Ertas B, Alenezi H et al (2021) Accelerated diabetic wound healing by topical application of combination oral antidiabetic agents-loaded nanofibrous scaffolds: an in vitro and in vivo evaluation study. Mater Sci Eng C 119:111586. https://doi.org/10.1016/j.msec.2020.111586

Cao G, Xiang C, Zhou R et al (2022) Notoginsenoside R1 facilitated wound healing in high-fat diet/streptozotocin-induced diabetic rats. Oxid Med Cell Longev. https://doi.org/10.1155/2022/2476493

Casqueiro J, Casqueiro J, Alves C (2012) Infections in patients with diabetes mellitus: a review of pathogenesis. Indian J Endocrinol Metab 16:27. https://doi.org/10.4103/2230-8210.94253

Chakraborty T, Gupta S, Nair A et al (2021) Wound healing potential of insulin-loaded nanoemulsion with Aloe vera gel in diabetic rats. J Drug Deliv Sci Technol 64:102601. https://doi.org/10.1016/j.jddst.2021.102601

Chandran R, Abrahamse H, Parimelazhagan T, Durai G (2017) *Syzygium mundagam* bark methanol extract restores skin to normal in diabetic wounded rats. Biomed Pharmacother 94:781–786. https://doi.org/10.1016/j.biopha.2017.07.114

Chen X, Liu Y, Zhang X (2012) Topical insulin application improves healing by regulating the wound inflammatory response. Wound Repair Regen 20:425–434. https://doi.org/10.1111/j.1524-475X.2012.00792.x

Chen CY, Wu RW, Hsu MC et al (2017) Adjunctive hyperbaric oxygen therapy for healing of chronic diabetic foot ulcers: a randomized controlled trial. J Wound, Ostomy Cont Nurs 44:536–545. https://doi.org/10.1097/WON.0000000000000374

Chen RF, Chang CH, Wang CT et al (2019) Modulation of vascular endothelial growth factor and mitogen-activated protein kinase-related pathway involved in extracorporeal shockwave therapy accelerate diabetic wound healing. Wound Repair Regen 27:69–79. https://doi.org/10.1111/wrr.12686

Chen LY, Huang CN, Liao CK et al (2020) Effects of rutin on wound healing in hyperglycemic rats. Antioxidants 9:1–13. https://doi.org/10.3390/antiox9111122

Chen LY, Cheng HL, Kuan YH et al (2021) Therapeutic potential of luteolin on impaired wound healing in streptozotocin-induced rats. Biomedicines 9:1–13. https://doi.org/10.3390/biomedicines9070761

Chereddy KK, Lopes A, Koussoroplis S et al (2015) Combined effects of PLGA and vascular endothelial growth factor promote the healing of non-diabetic and diabetic wounds. Nanomed Nanotechnol Biol Med 11:1975–1984. https://doi.org/10.1016/j.nano.2015.07.006

Chinnasamy G, Chandrasekharan S, Bhatnagar S (2019) Biosynthesis of silver nanoparticles from *Melia azedarach*: enhancement of antibacterial, wound healing, antidiabetic and antioxidant activities. Int J Nanomed 14:9823–9836. https://doi.org/10.2147/IJN.S231340

Choi SM, Ryu HA, Lee KM et al (2016) Development of stabilized growth factor-loaded hyaluronate- collagen dressing (HCD) matrix for impaired wound healing. Biomater Res 20:1–7. https://doi.org/10.1186/s40824-016-0056-4

Choi JU, Lee SW, Pangeni R et al (2017) Preparation and in vivo evaluation of cationic elastic liposomes comprising highly skin-permeable growth factors combined with hyaluronic acid for enhanced diabetic wound-healing therapy. Acta Biomater 57:197–215. https://doi.org/10.1016/j.actbio.2017.04.034

Chokpaisarn J, Chusri S, Amnuaikit T et al (2017) Potential wound healing activity of *Quercus infectoria* formulation in diabetic rats. PeerJ 2017:1–16. https://doi.org/10.7717/peerj.3608

Choudhary M, Chhabra P, Tyagi A, Singh H (2021) Scar free healing of full thickness diabetic wounds: a unique combination of silver nanoparticles as antimicrobial agent, calcium alginate nanoparticles as hemostatic agent, fresh blood as nutrient/growth factor supplier and chitosan as base matrix. Int J Biol Macromol 178:41–52. https://doi.org/10.1016/j.ijbiomac.2021.02.133

Chumpolphant S, Suwatronnakorn M, Issaravanich S et al (2022) Polyherbal formulation exerts wound healing, anti-inflammatory, angiogenic and antimicrobial properties: potential role in the treatment of diabetic foot ulcers. Saudi J Biol Sci 29:103330. https://doi.org/10.1016/j.sjbs.2022.103330

Collings R, Freeman J, Latour JM, Paton J (2021) Footwear and insole design features for offloading the diabetic at risk foot—a systematic review and meta-analyses. Endocrinol Diabetes Metab 4:1–18. https://doi.org/10.1002/edm2.132

Corrêa ACL, Oliveira AKM, Dourado DM et al (2021) *Pouteria ramiflora* leaf extract on emulgel in wound healing activity in diabetic

rats. Braz J Biol 82:e239378. https://doi.org/10.1590/1519-6984.239378
Crovetti G, Martinelli G, Issi M et al (2004) Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci 30:145–151. https://doi.org/10.1016/j.transci.2004.01.004
Da Porto A, Miranda C, Brosolo G et al (2022) Nutritional supplementation on wound healing in diabetic foot: what is known and what is new? World J Diabetes 13:940–948. https://doi.org/10.4239/wjd.v13.i11.940
Daemi A, Lotfi M, Farahpour MR et al (2019) Topical application of Cinnamomum hydroethanolic extract improves wound healing by enhancing re-epithelialization and keratin biosynthesis in streptozotocin-induced diabetic mice topical application of Cinnamomum hydroethanolic extract improves wound heal. Pharm Biol 57:799–806. https://doi.org/10.1080/13880209.2019.1687525
Dasari N, Jiang A, Skochdopole A et al (2021) Updates in diabetic wound healing, inflammation, and scarring. Semin Plast Surg 35:153–158. https://doi.org/10.1055/s-0041-1731460
Davis SC, Harding A, Gil J et al (2017) Effectiveness of a polyhexanide irrigation solution on methicillin-resistant *Staphylococcus aureus* biofilms in a porcine wound model. Int Wound J 14:937–944. https://doi.org/10.1111/iwj.12734
Dayya D, O'Neill OJ, Huedo-Medina TB et al (2022) Debridement of diabetic foot ulcers. Adv Wound Care 11:666–686. https://doi.org/10.1089/wound.2021.0016
de Sousa RG, Batista KNM (2016) Laser therapy in wound healing associated with diabetes mellitus - review. An Bras Dermatol 91:489–493. https://doi.org/10.1590/abd1806-4841.20163778
De Souza de Aguiar P, Correa ÁP, Antunes FTT et al (2021) Benefits of *Stryphnodendron adstringens* when associated with hydrogel on wound healing in diabetic rats. Clin Phytosci. https://doi.org/10.1186/s40816-021-00257-5
Debnath P, Health MPP, Prakash A et al (2014) Quality of life and treatment satisfaction observed among Indians with diabetes foot ulcers undergoing ayurvedic adjunct therapy. J Evid-Based Complement Altern Med. https://doi.org/10.1177/2156587214553304
Devalliere J, Dooley K, Yu Y et al (2017) Co-delivery of a growth factor and a tissue-protective molecule using elastin biopolymers accelerates wound healing in diabetic mice. Biomaterials 141:149–160. https://doi.org/10.1016/j.biomaterials.2017.06.043
Dhall S, Silva JP, Liu Y et al (2015) Release of insulin from PLGA-alginate dressing stimulates regenerative healing of burn wounds in rats. Clin Sci 129:1115–1129. https://doi.org/10.1042/CS20150393
Dik Burak BAL (2016) The effect of Midkine on growth factors and oxidative status in an experimental wound model in diabetic and healthy rats. Can J Physiol Pharmacol 90:1–24
Diovu EO, Ayoka TO, Onah CM et al (2023) Biochemical and histological insights of 1,4-polyisoprene isolated from *Sphenocentrum jollyanum* pierre (menispermaceae) stem in wound healing activity in streptozotocin-induced diabetic rats. J Ethnopharmacol 307:1–5. https://doi.org/10.1016/j.jep.2023.116248
Dos Santos VLP, Ribas JLC, de Lima CP et al (2020) The wound healing effect of aqueous extract from *Piper amalago* L. in diabetic patient. Explore 16:368–371. https://doi.org/10.1016/j.explore.2019.12.001
Doxey DL, Ng MC, Dill RE, Iacopino AM (1995) Platelet-derived growth factor levels in wounds of diabetic rats. Life Sci 57:1111–1123. https://doi.org/10.1016/0024-3205(95)02056-O
Du F, Liu M, Wang J et al (2023) Metformin coordinates with mesenchymal cells to promote VEGF-mediated angiogenesis in diabetic wound healing through Akt/mTOR activation. Metabolism. https://doi.org/10.1016/j.metabol.2023.155398
Dudhamal T, Gupta S, Mahanta V, Ajmeer A (2014) Katupila Securinega leucopyrus as a potential option for diabetic wound management. J Ayurveda Integr Med 5:60. https://doi.org/10.4103/0975-9476.128872
Dwita LP, Hasanah F, Srirustami R et al (2019) Wound healing properties of *Epiphyllum oxypetalum* (DC.) Haw. leaf extract in streptozotocin-induced diabetic mice by topical application. Wound Med 26:100160. https://doi.org/10.1016/j.wndm.2019.100160
El Hage R, Knippschild U, Arnold T, Hinterseher I (2022) Stem cell-based therapy: a promising treatment for diabetic foot ulcer. Biomedicines 10:1–22. https://doi.org/10.3390/biomedicines10071507
El Sayed AM, Ezzat SM, El Naggar MM, El Hawary SS (2016) In vivo diabetic wound healing effect and HPLC–DAD–ESI–MS/MS profiling of the methanol extracts of eight Aloe species. Rev Bras Farmacogn 26:352–362. https://doi.org/10.1016/j.bjp.2016.01.009
Elnahas RA, Elwakil BH, Elshewemi SS, Olama ZA (2021) Egyptian *Olea europaea* leaves bioactive extract: antibacterial and wound healing activity in normal and diabetic rats. J Tradit Complement Med. https://doi.org/10.1016/j.jtcme.2021.02.008
Elraiyah T, Domecq JP, Prutsky G et al (2016) A systematic review and meta-analysis of débridement methods for chronic diabetic foot ulcers. J Vasc Surg 63:37S.e2-45S.e2. https://doi.org/10.1016/j.jvs.2015.10.002
Erdoğan A, Düzgün AP, Erdoğan K et al (2018) Efficacy of hyperbaric oxygen therapy in diabetic foot ulcers based on Wagner classification. J Foot Ankle Surg 57:1115–1119. https://doi.org/10.1053/j.jfas.2018.05.011
Everett E, Mathioudakis N (2018) Update on management of diabetic foot ulcers. Ann N Y Acad Sci 1411:153–165. https://doi.org/10.1111/nyas.13569
Ezhilarasu H, Vishalli D, Dheen ST et al (2020) Nanoparticle-based therapeutic approach for diabetic wound healing. Nanomaterials 10:1–29. https://doi.org/10.3390/nano10061234
Fallah Huseini H, Abdolghaffari AH, Ahwazi M et al (2020) Topical application of *Teucrium polium* can improve wound healing in diabetic rats. Int J Low Extrem Wounds 19:132–138. https://doi.org/10.1177/1534734619868629
Fan SL, Lin JA, Chen SY et al (2021) Effects of Hsian-tsao (: *Mesona procumbens* Hemsl.) extracts and its polysaccharides on the promotion of wound healing under diabetes-like conditions. Food Funct 12:119–132. https://doi.org/10.1039/d0fo02180f
Fang W, Lan CE (2023) The epidermal keratinocyte as a therapeutic target for management of diabetic wounds
Fei J, Ling YM, Zeng MJ, Zhang KW (2019) Shixiang plaster, a traditional Chinese medicine, promotes healing in a rat model of diabetic ulcer through the receptor for advanced glycation end products (RAGE)/nuclear factor kappa B (NF-kB) and vascular endothelial growth factor (VEGF)/vascular cell. Med Sci Monit 25:9446–9457. https://doi.org/10.12659/MSM.918268
Frank S, Hubner G, Breier G et al (1995) Regulation of vascular endothelial growth factor expression in cultured keratinocytes. Implications for normal and impaired wound healing. J Biol Chem 270:12607–12613
Galehdari H, Negahdari S, Kesmati M et al (2016) Effect of the herbal mixture composed of Aloe vera, Henna, Adiantum capillus-veneris, and Myrrha on wound healing in streptozotocin-induced diabetic rats. BMC Complement Altern Med 16:1–9. https://doi.org/10.1186/s12906-016-1359-7
Galiano RD, Tepper OM, Pelo CR et al (2004) Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells. Am J Pathol 164:1935–1947. https://doi.org/10.1016/S0002-9440(10)63754-6

Gaonkar VP, Hullatti K (2020) Indian traditional medicinal plants as a source of potent anti-diabetic agents: a review. J Diabetes Metab Disorders 19:1895–1908

Gautam MK, Goel RK (2013) Wound healing effect of *Ocimum sanctum* leaves extract in diabetic rats. Int J Med Health Biomed Bioeng Pharm Eng 7:224–227

Gautam A, Kumar V, Azmi L et al (2023) Wound healing activity of the flavonoid-enriched fraction of *Selaginella bryopteris* Linn. against streptozocin-induced diabetes in rats. Separations 10:166

Getahun A, Kifle ZD, Ambikar D, Atnafie SA (2021) In vivo evaluation of 80% methanolic leaves crude extract and solvent fractions of *Buddleja polystachya* fresen (buddlejaceae) for wound healing activity in normal and diabetic mice. Metab Open 11:100110. https://doi.org/10.1016/j.metop.2021.100110

Ghanadian M, Soltani R, Homayouni A et al (2022) The effect of plantago major hydroalcoholic extract on the healing of diabetic foot and pressure ulcers: a randomized open-label controlled clinical trial. Int J Low Extrem Wounds. https://doi.org/10.1177/15347346211070723

Gharaboghaz MN, Farahpour MR, Saghaie S (2020) Topical co-administration of *Teucrium polium* hydroethanolic extract and Aloe vera gel triggered wound healing by accelerating cell proliferation in diabetic mouse model. Biomed Pharmacother 127:110189. https://doi.org/10.1016/j.biopha.2020.110189

Ghazali NA, Elmy A, Yuen LC et al (2016) Piper betel leaves induces wound healing activity via proliferation of fibroblasts and reducing 11β hydroxysteriod dehydrogenase-1 expression in diabetic rat. J Ayurveda Integr Med 7:198–208. https://doi.org/10.1016/j.jaim.2016.08.008

Gökalp Özkorkmaz E (2018) Ultrastructural examinations on diabetic rat skin tissue with topical application of Salvia euphratica ethanol extract. Int J Health Serv Res Policy 3:107–116. https://doi.org/10.23884/ijhsrp.2018.3.3.02

Gonzalez IG, Angel MAL, Baez MVJ et al (2017) Handcrafted vacuum-assisted device for skin ulcers treatment versus traditional therapy, randomized controlled trial. World J Surg 41:386–393. https://doi.org/10.1007/s00268-016-3782-9

Gooyit M, Peng Z, Wolter WR et al (2014) A chemical biological strategy to facilitate diabetic wound healing. ACS Chem Biol 9:105–110. https://doi.org/10.1021/cb4005468

Gordon AJ, Alfonso AR, Nicholson J, Chiu ES (2019) Evidence for healing diabetic foot ulcers with biologic skin substitutes: a systematic review and meta-analysis. Ann Plast Surg 83:S31–S44. https://doi.org/10.1097/SAP.0000000000002096

Gowda A, Shanbhag V, Shenoy S et al (2013) Wound healing property of topical application of ethanolic extract of *Michelia champaca* flowers in diabetic rats. Int J Pharmacol Clin Sci Sept 2:67–74

Grande R, Fiori G, Russo G et al (2020) A multistage combined approach to promote diabetic wound healing in COVID-19 era. Int Wound J 17:1863–1870. https://doi.org/10.1111/iwj.13476

Greenhalgh DG, Sprugel KH, Murray MJ, Ross R (1990) PDGF and FGF stimulate wound healing in the genetically diabetic mouse. Am J Pathol 136:1235–1246

Güiza-Argüello VR, Solarte-David VA, Pinzón-Mora AV et al (2022) Current advances in the development of hydrogel-based wound dressings for diabetic foot ulcer treatment. Polymers (basel) 14:1–25. https://doi.org/10.3390/polym14142764

Guo J, Hu Z, Yan F et al (2020) Angelica dahurica promoted angiogenesis and accelerated wound healing in db/db mice via the HIF-1α/PDGF-β signaling pathway. Free Radic Biol Med 160:447–457. https://doi.org/10.1016/j.freeradbiomed.2020.08.015

Güzel S, Özay Y, Kumaş M et al (2019) Wound healing properties, antimicrobial and antioxidant activities of *Salvia kronenburgii* Rech. f. and *Salvia euphratica* Montbret, Aucher & Rech. f. var. euphratica on excision and incision wound models in diabetic rats. Biomed Pharmacother 111:1260–1276. https://doi.org/10.1016/j.biopha.2019.01.038

Hajialyani M, Tewari D, Sobarzo-Sánchez E et al (2018) Natural product-based nanomedicines for wound healing purposes: therapeutic targets and drug delivery systems. Int J Nanomed 13:5023–5043. https://doi.org/10.2147/IJN.S174072

Hamza RZ, Al-motaani SE, Al-talhi T (2021) Therapeutic and ameliorative effects of active compounds of combretum molle in the treatment and relief from wounds in a diabetes mellitus experimental model. Coatings. https://doi.org/10.3390/coatings11030324

Han G, Ceilley R (2017) Chronic wound healing: a review of current management and treatments. Adv Ther 34:599–610. https://doi.org/10.1007/s12325-017-0478-y

Han X, Tao Y, Deng Y et al (2017) Metformin accelerates wound healing in type 2 diabetic db/db mice. Mol Med Rep 16:8691–8698. https://doi.org/10.3892/mmr.2017.7707

Han L, Yu J, Chen Y et al (2018) Immunomodulatory activity of docosahexenoic acid on RAW264.7 cells activation through GPR120-mediated signaling pathway. J Agric Food Chem 66:926–934. https://doi.org/10.1021/acs.jafc.7b05894

Hardwicke JT, Hart J, Bell A et al (2011) The effect of dextrin-rhEGF on the healing of full-thickness, excisional wounds in the (db/db) diabetic mouse. J Control Release 152:411–417. https://doi.org/10.1016/j.jconrel.2011.03.016

Hashemnia M, Nikousefat Z, Mohammadalipour A et al (2019) Wound healing activity of Pimpinella anisum methanolic extract in streptozotocin-induced diabetic rats. J Wound Care 28:S26–S36. https://doi.org/10.12968/jowc.2019.28.sup10.s26

Haycocks S, Chadwick P (2012) Debridement of diabetic foot wounds. Nurs Stand 26:51–58. https://doi.org/10.7748/ns2012.02.26.24.51.c8947

Herman A, Herman AP (2023) Herbal products and their active constituents for diabetic wound healing—preclinical and clinical studies: a systematic review. Pharmaceutics. https://doi.org/10.3390/pharmaceutics15010281

Hernandez-Hernandez AB, Alarcon-Aguilar FJ, Garcia-Lorenzana M et al (2021) *Jatropha neopauciflora* Pax Latex exhibits wound-healing effect in normal and diabetic mice. J Evid-Based Integr Med 26:1–10. https://doi.org/10.1177/2515690X20986762

Herowati R, Saputri ADS, Wijayanti T, Widodo GP (2018) Antihyperglycemic and diabetic wound healing activity of *Smallanthus sonchifolius* leaves extract. MATEC Web Conf 197:1–5. https://doi.org/10.1051/matecconf/201819707001

Heublein H, Bader A, Giri S (2015) Preclinical and clinical evidence for stem cell therapies as treatment for diabetic wounds. Drug Discov Today 20:703–717. https://doi.org/10.1016/j.drudis.2015.01.005

Hirase T, Ruff E, Surani S, Ratnani I (2018) Topical application of platelet-rich plasma for diabetic foot ulcers: a systematic review. World J Diabetes 9:172–179. https://doi.org/10.4239/wjd.v9.i10.172

Hosokawa R, Kikuzaki K, Kimoto T et al (2000) Controlled local application of basic fibroblast growth factor (FGF-2) accelerates the healing of GBR - an experimental study in beagle dogs. Clin Oral Implants Res 11:345–353. https://doi.org/10.1034/j.1600-0501.2000.011004345.x

Hosseini Mansoub N (2022) The role of keratinocyte function on the defected diabetic wound healing. Clin Diabetol 11:430–441. https://doi.org/10.5603/dk.a2022.0004

Houreld N, Abrahamse H (2007) Irradiation with a 632.8 nm helium-neon laser with 5 J/cm2 stimulates proliferation and expression of interleukin-6 in diabetic wounded fibroblast cells. Diabetes Technol Ther 9:451–459. https://doi.org/10.1089/dia.2007.0203

Hozzein WN, Badr G, Al Ghamdi AA et al (2015) Topical application of propolis enhances cutaneous wound healing by promoting TGF-beta/smad-mediated collagen production in a streptozotocin-induced type I diabetic mouse model. Cell Physiol Biochem 37:940–954. https://doi.org/10.1159/000430221

Hussan F, Teoh SL, Muhamad N et al (2014) Momordica charantia ointment accelerates diabetic wound healing and enhances transforming growth factor-β expression. J Wound Care 23:400–407. https://doi.org/10.12968/jowc.2014.23.8.400

Hyun S-W, Kim J, Jo K et al (2018) *Aster koraiensis* extract improves impaired skin wound healing during hyperglycemia. Integr Med Res 7:351–357. https://doi.org/10.1016/j.imr.2018.09.001

Icli B, Nabzdyk CS, Lujan-Hernandez J et al (2016) Regulation of impaired angiogenesis in diabetic dermal wound healing by microRNA-26a. J Mol Cell Cardiol 91:151–159. https://doi.org/10.1016/j.yjmcc.2016.01.007

Ilmi ZN, Wulandari PAC, Husen SA et al (2020) Characterization of alginate from *Sargassum duplicatum* and the antioxidant effect of alginate-okra fruit extracts combination for wound healing on diabetic mice. Appl Sci. https://doi.org/10.3390/app10176082

Jacob J, Harindran J, Jessy Jacob C, Aleykutty N (2017) Evaluation of wound healing activity in streptozotocin induced diabetic rats by ethanolic extract of *Blepharis maderaspatensis* (L.) B. Heyne ex Roth. Int J Herb Med 5:45–47

Jagadeep Chandra S, Mahadeva Murthy S, Ramesh R (2017) Evaluation of the wound healing activity of *Caesalpinia bonducella* and *Cyclea peltata* extracts in experimentally induced diabetic rats. Int J Pharm Pharm Sci 9:211. https://doi.org/10.22159/ijpps.2017v9i10.19788

Jameeluddin M, Janarthan M, Duraivel S (2014) Evaluation of antidiabetic and wound healing activities of 90 % methanolic extract of *Ficus mollis* bark by using wistar strain rats. Indian J Res Pharm Biotechnol 5674:988–992

Jayalakshmi MS, Thenmozhi P, Vijayaraghavan R (2021) Plant leaves extract irrigation on wound healing in diabetic foot ulcers. Evid-Based Complement Altern Med. https://doi.org/10.1155/2021/9924725

Ji S, Liu X, Huang J et al (2021) Consensus on the application of negative pressure wound therapy of diabetic foot wounds. Burn Trauma. https://doi.org/10.1093/burnst/tkab018

Ji JY, Ren DY, Weng YZ (2022) Efficiency of multifunctional antibacterial hydrogels for chronic wound healing in diabetes: a comprehensive review. Int J Nanomed 17:3163–3176. https://doi.org/10.2147/IJN.S363827

Johani K, Malone M, Jensen SO et al (2018) Evaluation of short exposure times of antimicrobial wound solutions against microbial biofilms: from in vitro to in vivo. J Antimicrob Chemother 73:494–502. https://doi.org/10.1093/jac/dkx391

Jude EB, Blakytny R, Bulmer J et al (2002) Transforming growth factor-beta 1, 2, 3 and receptor type I and II in diabetic foot ulcers. Diabet Med 19:440–447. https://doi.org/10.1046/j.1464-5491.2002.00692.x

Jung JA, Yoo KH, Han SK et al (2016) Influence of Negative-Pressure Wound Therapy on Tissue Oxygenation in Diabetic Feet. Adv Ski Wound Care 29:364–370. https://doi.org/10.1097/01.ASW.0000483038.18331.a4

Kairinos N, Holmes WJM, Solomons M et al (2013) Does a zone of increased perfusion exist around negative-pressure dressings? Plast Reconstr Surg 132:978–987. https://doi.org/10.1097/PRS.0b013e31829f4ad9

Kamaratos AV, Tzirogiannis KN, Iraklianou SA et al (2014) Manuka honey-impregnated dressings in the treatment of neuropathic diabetic foot ulcers. Int Wound J 11:259–263. https://doi.org/10.1111/j.1742-481X.2012.01082.x

Kamel R, Elmotasem H, Abdelsalam E, Salama A (2021) *Lepidium sativum* seed oil 3D nano-oleogel for the management of diabetic wounds: GC/MS analysis, in-vitro and in-vivo studies. J Drug Deliv Sci Technol 63:102504. https://doi.org/10.1016/j.jddst.2021.102504

Kandimalla R, Kalita S, Choudhury B et al (2016) Chemical composition and anti-candidiasis mediated wound healing property of *Cymbopogon nardus* essential oil on chronic diabetic wounds. Front Pharmacol 7:1–8. https://doi.org/10.3389/fphar.2016.00198

Kant V, Gopal A, Pathak NN et al (2014) Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats. Int Immunopharmacol 20:322–330. https://doi.org/10.1016/j.intimp.2014.03.009

Kant V, Kumar D, Prasad R et al (2017) Combined effect of substance P and curcumin on cutaneous wound healing in diabetic rats. J Surg Res 212:130–145. https://doi.org/10.1016/j.jss.2017.01.011

Kant V, Jangir BL, Sharma M et al (2021) Topical application of quercetin improves wound repair and regeneration in diabetic rats. Immunopharmacol Immunotoxicol 43:536–553. https://doi.org/10.1080/08923973.2021.1950758

Karim S, Alkreathy HM, Ahmad A, Khan MI (2021) Effects of methanolic extract based-gel from Saudi pomegranate peels with enhanced healing potential on excision wounds in diabetic rats. Front Pharmacol 12:1–12. https://doi.org/10.3389/fphar.2021.704503

Karonova T, Stepanova A, Bystrova A, Jude EB (2020) Microcirculation and reduces inflammation in diabetic neuropathy patients. Nutrients 12:2518

Kartini K, Wati N, Gustav R et al (2021) Wound healing effects of Plantago major extract and its chemical compounds in hyperglycemic rats. Food Biosci 41:100937. https://doi.org/10.1016/j.fbio.2021.100937

Kaviani A, Djavid GE, Ataie-Fashtami L et al (2011) A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. Photomed Laser Surg 29:109–114. https://doi.org/10.1089/pho.2009.2680

Kavitha KV (2014) Choice of wound care in diabetic foot ulcer: a practical approach. World J Diabetes 5:546. https://doi.org/10.4239/wjd.v5.i4.546

Khan MA, Shahzadi T, Malik SA et al (2019) Pharmacognostic evaluation of turmeric (*Curcuma longa*) extracts in diabetic wound healing. J Anim Plant Sci 29:68–74

Khodaie S-A, Emadi F, Naseri M et al (2020) The effect of *Myrtus communis* aqueous extract-containing gel on wound healing in streptozotocin-induced diabetic rats. Curr Drug Discov Technol 18:542–547. https://doi.org/10.2174/1570163817666200712163956

Kim SW, Zhang HZ, Guo L et al (2012) Amniotic mesenchymal stem cells enhance wound healing in diabetic NOD/SCID mice through high angiogenic and engraftment capabilities. PLoS ONE 7:1–11. https://doi.org/10.1371/journal.pone.0041105

Kim DW, Jo YY, Garagiola U et al (2020) Increased level of vascular endothelial growth factors by 4-hexylresorcinol is mediated by transforming growth factor-β1 and accelerates capillary regeneration in the burns in diabetic animals. Int J Mol Sci 21:1–10. https://doi.org/10.3390/ijms21103473

Kim TJ, Pyun DH, Park SY et al (2021) Patchouli alcohol improves wound healing in high fat diet-fed mice through AMPK-mediated suppression of inflammation and TGFb1 signaling. Biochem Biophys Res Commun 561:136–142. https://doi.org/10.1016/j.bbrc.2021.05.036

Kirana S, Stratmann B, Prante C et al (2012) Autologous stem cell therapy in the treatment of limb ischaemia induced chronic tissue ulcers of diabetic foot patients. Int J Clin Pract 66:384–393. https://doi.org/10.1111/j.1742-1241.2011.02886.x

Kostadinova L, Shive CL, Anthony DD (2019) Elevated autotaxin and LPA levels during chronic viral hepatitis and hepatocellular

carcinoma associate with systemic immune activation. Cancers (Basel) 11:1867. https://doi.org/10.3390/cancers11121867
Kulprachakarn K, Ounjaijean S, Wungrath J et al (2017) Micronutrients and natural compounds status and their effects on wound healing in the diabetic foot ulcer. Int J Low Extrem Wounds 16:244–250. https://doi.org/10.1177/1534734617737659
Kumar V et al (2012) Comparative study of hypoglycemic and hypolipidemic potency of *Murraya koenigii* for wound healing activity in type-2 diabetic rats. Int JPharm Bio Sci 2:150–161
Kumar A, Wang X, Nune KC, Misra RDK (2017a) Biodegradable hydrogel-based biomaterials with high absorbent properties for non-adherent wound dressing. Int Wound J 14:1076–1087. https://doi.org/10.1111/iwj.12762
Kumar RS, Rajkiran K, Patnaik SK (2017b) Evaluation of incisional diabetic wound healing activity of ethanolic leave extract of *Mimosa pudica* L. in rats. Int J Pharmacogn Phytochem Res 9:1143–1147. https://doi.org/10.2525/phyto.v9i08.9623
Kumar SSD, Houreld NN, Abrahamse H (2020) Selective laser efficiency of green-synthesized silver nanoparticles by aloe arborescens and its wound healing activities in normal wounded and diabetic wounded fibroblast cells: in vitro studies. Int J Nanomed 15:6855–6870. https://doi.org/10.2147/IJN.S257204
Kumari SJ, Sangeetha M, Ali S (2018) Formulation and evaluation of herbal gel from tannin-enriched fraction of *Psidium guajava* Linn. leaves for diabetic wound healing. Int J Green Pharm 12:S490–S496
Kuo YS, Chien HF, Lu W (2012) *Plectranthus amboinicus* and *Centella asiatica* cream for the treatment of diabetic foot ulcers. Evid-Based Complement Altern Med. https://doi.org/10.1155/2012/418679
Lau KM, Lai KK, Liu CL et al (2012) Synergistic interaction between *Astragali radix* and *Rehmanniae radix* in a Chinese herbal formula to promote diabetic wound healing. J Ethnopharmacol 141:250–256. https://doi.org/10.1016/j.jep.2012.02.025
Lázaro-Martínez JL, Álvaro-Afonso FJ, Sevillano-Fernández D et al (2020) Cellular proliferation, dermal repair, and microbiological effectiveness of ultrasound-assisted wound debridement (UAW) versus standard wound treatment in complicated diabetic foot ulcers (DFU): an open-label randomized controlled trial. J Clin Med 9:1–13. https://doi.org/10.3390/jcm9124032
Lee YH, Hong YL, Wu TL (2021) Novel silver and nanoparticle-encapsulated growth factor co-loaded chitosan composite hydrogel with sustained antimicrobility and promoted biological properties for diabetic wound healing. Mater Sci Eng C 118:111385. https://doi.org/10.1016/j.msec.2020.111385
Lei J, Chen P, Li Y et al (2017) Collagen hydrogel dressing for wound healing and angiogenesis in diabetic rat models. Int J Clin Exp Med 10:16319–16327
Li H, Fu X, Zhang L et al (2008) Research of PDGF-BB gel on the wound healing of diabetic rats and its pharmacodynamics. J Surg Res 145:41–48. https://doi.org/10.1016/j.jss.2007.02.044
Li S, Zhao J, Liu J et al (2011) Prospective randomized controlled study of a Chinese herbal medicine compound Tangzu Yuyang ointment for chronic diabetic foot ulcers: a preliminary report. J Ethnopharmacol 133:543–550. https://doi.org/10.1016/j.jep.2010.10.040
Li Z, Guo S, Yao F et al (2013) Increased ratio of serum matrix metalloproteinase-9 against TIMP-1 predicts poor wound healing in diabetic foot ulcers. J Diabetes Complicat 27:380–382. https://doi.org/10.1016/j.jdiacomp.2012.12.007
Li X, Xie X, Lian W et al (2018) Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model. Exp Mol Med. https://doi.org/10.1038/s12276-018-0058-5
Li J, Chou H, Li L et al (2020) Wound healing activity of neferine in experimental diabetic rats through the inhibition of inflammatory cytokines and nrf-2 pathway. Artif Cells Nanomed Biotechnol 48:96–106. https://doi.org/10.1080/21691401.2019.1699814
Lin CW, Hung CM, Chen WJ et al (2022) New horizons of macrophage immunomodulation in the healing of diabetic foot ulcers. Pharmaceutics 14:1–15. https://doi.org/10.3390/pharmaceutics14102065
Lipsky BA, Aragón-Sánchez J, Diggle M et al (2016) IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev 32:45–74. https://doi.org/10.1002/dmrr.2699
Liu S, He C, Cai Y et al (2017) Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis. Ther Clin Risk Manag 13:533–544. https://doi.org/10.2147/TCRM.S131193
Liu H, Zhao Y, Zou Y et al (2019) Heparin-poloxamer hydrogel-encapsulated rhFGF21 enhances wound healing in diabetic mice. FASEB J 33:9858–9870. https://doi.org/10.1096/fj.201802600RR
Liu Y, Zeng S, Ji W et al (2022) Emerging theranostic nanomaterials in diabetes and its complications. Adv Sci 9:1–54. https://doi.org/10.1002/advs.202102466
Lobmann R, Zemlin C, Motzkau M et al (2006) Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. J Diabetes Complicat 20:329–335. https://doi.org/10.1016/j.jdiacomp.2005.08.007
Lodhi S, Singhai AK (2013) Wound healing effect of flavonoid rich fraction and luteolin isolated from *Martynia annua* Linn. on streptozotocin induced diabetic rats. Asian Pac J Trop Med 6:253–259. https://doi.org/10.1016/S1995-7645(13)60053-X
Lodhi S, Jain AP, Sharma VK, Singhai AK (2013) Wound-healing effect of flavonoid-rich fraction from *Tephrosia purpurea* Linn. on streptozotocin-induced diabetic rats. J Herbs Spices Med Plants 19:191–205. https://doi.org/10.1080/10496475.2013.779620
Loots MAM, Kenter SB, Au FL et al (2002) Fibroblasts derived from chronic diabetic ulcers differ in their response to stimulation with EGF, IGF-I, bFGF and PDGF-AB compared to controls. Eur J Cell Biol 81:153–160. https://doi.org/10.1078/0171-9335-00228
Lwin OM, Giribabu N, Kilari EK, Salleh N (2021) Topical administration of mangiferin promotes healing of the wound of streptozotocin-nicotinamide-induced type-2 diabetic male rats. J Dermatol Treat 32:1039–1048. https://doi.org/10.1080/09546634.2020.1721419
Maiya GA, Kumar P, Rao L (2005) Effect of low intensity helium-neon (He-Ne) laser irradiation on diabetic wound healing dynamics. Photomed Laser Surg 23:187–190. https://doi.org/10.1089/pho.2005.23.187
Mali RP, Rao PS, Vikhe DN (2020) Wound healing activity of calotropis procera root bark on diabetic rats. J Drug Deliv Ther 10:86–89. https://doi.org/10.22270/jddt.v10i2-s.3955
Malini DM, Kuntana YP, Madihah M et al (2020) Treatment of PLGA nanoparticles ointment-ethanol extract of *Archidendron pauciflorum* in the wound healing in diabetic mice. J Biodjati 5:214–222. https://doi.org/10.1557/biodjati.v5i2.9256
Mancini S, Cuomo R, Poggialini M et al (2017) Autolytic debridement and management of bacterial load with an occlusive hydroactive deressing impregnated with polyhexamethylene biguanide. Acta Biomed 88:409–413. https://doi.org/10.23750/abm.v88i4.5802
Mandrika I, Kumar S, Zandersone B et al (2021) Antibacterial and anti-inflammatory potential of polyherbal formulation used in chronic wound healing. Evid-Based Complement Altern Med
Manne AA, Arigela B, Giduturi AK et al (2021) *Pterocarpus marsupium* Roxburgh heartwood extract/chitosan nanoparticles loaded

hydrogel as an innovative wound healing agent in the diabetic rat model. Mater Today Commun 26:101916. https://doi.org/10.1016/j.mtcomm.2020.101916

Marchianti ACN, Sakinah EN, Elfiah U et al (2021) Gel formulations of *Merremia mammosa* (Lour.) accelerated wound healing of the wound in diabetic rats. J Tradit Complement Med 11:38–45. https://doi.org/10.1016/j.jtcme.2019.12.002

Mariadoss AVA, Park S, Saravanakumar K et al (2021) Ethyl acetate fraction of *Helianthus tuberosus* l. Induces anti-diabetic, and wound-healing activities in insulin-resistant human liver cancer and mouse fibroblast cells. Antioxidants 10:1–22. https://doi.org/10.3390/antiox10010099

Maruyama K, Asai J, Ii M et al (2007) Decreased macrophage number and activation lead to reduced lymphatic vessel formation and contribute to impaired diabetic wound healing. Am J Pathol 170:1178–1191. https://doi.org/10.2353/ajpath.2007.060018

Mazumdar S, Ghosh AK, Dinda M et al (2021) Evaluation of wound healing activity of ethanol extract of *Annona reticulata* L. leaf both in vitro and in diabetic mice model. J Tradit Complement Med 11:27–37. https://doi.org/10.1016/j.jtcme.2019.12.001

Mehrannia M, Vaezi M, Yousefshahi F, Rouhipour N (2014) Platelet rich plasma for treatment of nonhealing diabetic foot ulcers: a case report. Can J Diabetes 38:5–8. https://doi.org/10.1016/j.jcjd.2013.08.271

Melotto G, Tunprasert T, Forss JR (2022) The effects of electrical stimulation on diabetic ulcers of foot and lower limb: a systematic review. Int Wound J 19:1911–1933. https://doi.org/10.1111/iwj.13762

Merbawani R, Ragil Saputri NH, Munfadlila AW (2019) Effectiveness of therapy topical binahong leaf extract in modern wound care for healing diabetic wounds in modern wound care homes Husada Prima Mandiri Mojokerto. Int J Nurs Midwifery Sci 2:234–243. https://doi.org/10.29082/ijnms/2018/vol2/iss03/179

Michael M, Anyakudo C, Erinfolami AB (2015) Glycemic and wound healing effects of aqueous mesocarp extract of unripe *Carica papaya* (Linn) in diabetic and healthy rats. World J Nutr Health 3:47–52. https://doi.org/10.12691/jnh-3-3-1

Mohajeri G, Safaee M, Sanei MH (2014) Effects of topical kiwifruit on healing of neuropathic diabetic foot ulcer. J Res Med Sci 19:520–524

Mohanty C, Pradhan J (2020) A human epidermal growth factor-curcumin bandage bioconjugate loaded with mesenchymal stem cell for in vivo diabetic wound healing. Mater Sci Eng C 111:110751. https://doi.org/10.1016/j.msec.2020.110751

Mojally M, Sharmin E, Alhindi Y et al (2022) Hydrogel films of methanolic *Mentha piperita* extract and silver nanoparticles enhance wound healing in rats with diabetes Type I. J Taibah Univ Sci 16:308–316. https://doi.org/10.1080/16583655.2022.2054607

Moreira JAR, Vasconcelos IC, Fachi JL et al (2021) Application of *Solidago chilensis* and laser improved the repair of burns in diabetic rats. Biomed J 44:709–716. https://doi.org/10.1016/j.bj.2020.05.014

Moura J, Børsheim E, Carvalho E (2014) The role of micrornas in diabetic complications—special emphasis on wound healing. Genes (basel) 5:926–956. https://doi.org/10.3390/genes5040926

Muhammad AA, Arulselvan P, Cheah PS et al (2016) Evaluation of wound healing properties of bioactive aqueous fraction from *Moringa oleifera* Lam on experimentally induced diabetic animal model. Drug Des Devel Ther 10:1715–1730. https://doi.org/10.2147/DDDT.S96968

Mumtaz R, Zubair M, Khan MA et al (2022) Extracts of *Eucalyptus alba* promote diabetic wound healing by inhibiting α -glucosidase and stimulating cell proliferation. Evid-Based Complement Altern Med. https://doi.org/10.1155/2022/4953105

Najafian Y, Khorasani ZM, Najafi MN et al (2018) Efficacy of Aloe vera/ Plantago major gel in diabetic foot ulcer: a randomized double-blind clinical trial. Curr Drug Discov Technol 16:223–231. https://doi.org/10.2174/1570163815666180115093007

Naji S, Zarei L, Pourjabali M, Mohammadi R (2017) The Extract of *Lycium depressum* stocks enhances wound healing in streptozotocin-induced diabetic rats. Int J Low Extrem Wounds 16:85–93. https://doi.org/10.1177/1534734617700538

Namgoong S, Lee H, Han SK et al (2019) Effect of Panax ginseng extract on the activity of diabetic fibroblasts in vitro. Int Wound J 16:737–745. https://doi.org/10.1111/iwj.13091

Namgoong S, Jung SY, Han SK et al (2020) Clinical experience with surgical debridement and simultaneous meshed skin grafts in treating biofilm-associated infection: an exploratory retrospective pilot study. J Plast Surg Hand Surg 54:47–54. https://doi.org/10.1080/2000656X.2019.1673170

Nasiri M, Fayazi S, Jahani S et al (2015) The effect of topical olive oil on the healing of foot ulcer in patients with type 2 diabetes: a double-blind randomized clinical trial study in Iran. J Diabetes Metab Disord 14:1–10. https://doi.org/10.1186/s40200-015-0167-9

Nasiry D, Khalatbary AR, Ghaemi A et al (2022) Topical administration of *Juglans regia* L. leaf extract accelerates diabetic wound healing. BMC Complement Med Ther 22:1–12. https://doi.org/10.1186/s12906-022-03735-6

Nass N, Vogel K, Hofmann B et al (2010) Glycation of PDGF results in decreased biological activity. Int J Biochem Cell Biol 42:749–754. https://doi.org/10.1016/j.biocel.2010.01.012

Nematollahi P, Aref NM, Meimandi FZ et al (2019) Matricaria chamomilla extract improves diabetic wound healing in rat models. Trauma Mon. https://doi.org/10.5812/traumamon.14318

Nilforoushzadeh MA, Sisakht MM, Amirkhani MA et al (2020) Engineered skin graft with stromal vascular fraction cells encapsulated in fibrin–collagen hydrogel: a clinical study for diabetic wound healing. J Tissue Eng Regen Med 14:424–440. https://doi.org/10.1002/term.3003

Notodihardjo SC, Morimoto N, Munisso MC et al (2020) A comparison of the wound healing process after the application of three dermal substitutes with or without basic fibroblast growth factor impregnation in diabetic mice. J Plast Reconstr Aesthetic Surg 73:1547–1555. https://doi.org/10.1016/j.bjps.2020.01.031

Nwaehujor CO, Nwinyi CF, Igile GO (2013) The wound healing activities of Garcinia hydroxylbiflavanonol (GB1) from *Garcinia kola* in streptozotocin-induced diabetic rats. Photon 128:173–179

Oguntibeju OO (2019) Medicinal plants and their effects on diabetic wound healing. Vet World 12:653–663. https://doi.org/10.14202/vetworld.2019.653-663

Okizaki SI, Ito Y, Hosono K, et al (2015) Suppressed recruitment of alternatively activated macrophages reduces TGF-β1 and impairs wound healing in streptozotocin-induced diabetic mice. Biomed Pharmacother 70:317–325. https://doi.org/10.1016/j.biopha.2014.10.020

Ongarora BG (2022) Recent technological advances in the management of chronic wounds: a literature review. Health Sci Rep. https://doi.org/10.1002/hsr2.641

Ouyang L, Qiu D, Fu X et al (2022) Overexpressing HPGDS in adipose-derived mesenchymal stem cells reduces inflammatory state and improves wound healing in type 2 diabetic mice. Stem Cell Res Ther 13:1–15. https://doi.org/10.1186/s13287-022-03082-w

Oyebode O, Houreld NN, Abrahamse H (2021) Photobiomodulation in diabetic wound healing: a review of red and near-infrared wavelength applications. Cell Biochem Funct 39:596–612. https://doi.org/10.1002/cbf.3629

Ozay Y, Guzel S, Erdogdu IH et al (2018) Evaluation of the wound healing properties of luteolin ointments on excision and incision

wound models in diabetic and non-diabetic rats. Rec Nat Prod 12:350–366. https://doi.org/10.25135/rnp.38.17.08.135
Ozay Y, Guzel S, Gokalp Ozkorkmaz E et al (2021) Biochemical, histopathologic, and genotoxic effects of ethanol extract of *Salvia hypargeia* (Fisch. & Mey.) on incisional and excisional wounded diabetic rats. J Investig Surg 34:7–19. https://doi.org/10.1080/08941939.2019.1590483
Özay Y, Güzel S, Yumrutaş Ö et al (2019) Wound healing effect of kaempferol in diabetic and nondiabetic rats. J Surg Res 233:284–296. https://doi.org/10.1016/j.jss.2018.08.009
Park DH, Park JY, Shin M (2023) Wound healing effect of 20 (S) -protopanaxadiol of ginseng involves VEGF-ERK pathways in HUVECs and diabetic mice. Processes 11:692
Parkar MH, Kuru L, Giouzeli M, Olsen I (2001) Expression of growth-factor receptors in normal and regenerating human periodontal cells. Arch Oral Biol 46:275–284. https://doi.org/10.1016/S0003-9969(00)00099-6
Parmar KM, Shende PR, Katare N et al (2018) Wound healing potential of *Solanum xanthocarpum* in streptozotocin-induced diabetic rats. J Pharm Pharmacol 70:1389–1400. https://doi.org/10.1111/jphp.12975
Patel S, Srivastava S, Singh MR, Singh D (2019) Biomedicine & pharmacotherapy mechanistic insight into diabetic wounds: pathogenesis, molecular targets and treatment strategies to pace wound healing. Biomed Pharmacother 112:108615. https://doi.org/10.1016/j.biopha.2019.108615
Paul TS, Das BB, Talekar YP, Banerjee S (2020) Exploration of the role of a lithophytic fern, *Pteris vittata* L. in wound tissue regeneration and remodelling of genes in hyperglycaemic rat model. Clin Phytosci. https://doi.org/10.1186/s40816-020-00223-7
Pawar RS, Kumar S, Toppo FA et al (2016) *Sida cordifolia* Linn. accelerates wound healing process in type 2 diabetic rats. J Acute Med 6:82–89. https://doi.org/10.1016/j.jacme.2016.08.004
Pérez Gutiérrez RM, Muñiz Ramirez A (2013) Hexane extract of the seeds of *Byrsonima crassifolia* accelerates wound healing in streptozotocin-induced diabetic rats. Chin J Integr Med. https://doi.org/10.1007/s11655-013-1556-x
Perez-Favila A, Martinez-Fierro ML, Rodriguez-Lazalde JG et al (2019) Current therapeutic strategies in diabetic foot ulcers. Medicina 55:1–21. https://doi.org/10.3390/medicina55110714
Pessanha FS, Guitton B, Baptista R et al (2023) Effectiveness of epidermal growth factor loaded carboxymethylcellulose (EGF-CMC) hydrogel in biofilm formation in wounds of diabetic patients: a randomized clinical trial. Gels 9:117
Petchi RR, Vijaya C, Parasuraman S (2014) Antidiabetic activity of polyherbal formulation in streptozotocin – nicotinamide induced diabetic Wistar rats. J Tradit Complement Med 4:108–117. https://doi.org/10.4103/2225-4110.126174
Petkovic M, Sørensen AE, Leal EC et al (2020) Mechanistic actions of microRNAs in diabetic wound healing. Cells. https://doi.org/10.3390/cells9102228
Pis A, Altunkaynak BZ (2014) The beneficial effects of *Momordica charantia* (bitter gourd) on wound healing of rabbit skin. J Dermatol Treat. https://doi.org/10.3109/09546634.2012.713459
Ponnanikajamideen MI, Rajeshkumar S, Vanaja M, Annadurai G (2019) In vivo type 2 diabetes and wound-healing effects of antioxidant gold nanoparticles synthesized using the insulin plant *Chamaecostus cuspidatus* in Albino rats. Can J Diabetes 43:82-89.e6. https://doi.org/10.1016/j.jcjd.2018.05.006
Ponrasu T, Suguna L (2012) Efficacy of Annona squamosa on wound healing in streptozotocin-induced diabetic rats. Int Wound J 9:613–623. https://doi.org/10.1111/j.1742-481X.2011.00924.x
Pradhan L, Cai X, Wu S et al (2011) Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. J Surg Res 167:336–342. https://doi.org/10.1016/j.jss.2009.09.012
Prasathkumar M, Anisha S, Khusro A et al (2022) Anti-pathogenic, anti-diabetic, anti-inflammatory, antioxidant, and wound healing efficacy of *Datura metel* L. leaves. Arab J Chem 15:104112. https://doi.org/10.1016/j.arabjc.2022.104112
Presta LG, Chen H, O'Connor SJ et al (1997) Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 57:4593–4599
Qin W, Wu Y, Liu J et al (2022) A comprehensive review of the application of nanoparticles in diabetic wound healing: therapeutic potential and future perspectives. Int J Nanomedicine 17:6007–6029. https://doi.org/10.2147/IJN.S386585
Quazi A, Patwekar M, Patwekar F et al (2022) Evaluation of wound healing activity (excision wound model) of ointment prepared from infusion extract of polyherbal tea bag formulation in diabetes-induced rats. Evid-Based Complement Altern Med 2022:1–7. https://doi.org/10.1155/2022/1372199
Ram M, Singh V, Kumawat S et al (2015) Deferoxamine modulates cytokines and growth factors to accelerate cutaneous wound healing in diabetic rats. Elsevier
Ram M, Singh V, Kumawat S et al (2016) Bilirubin modulated cytokines, growth factors and angiogenesis to improve cutaneous wound healing process in diabetic rats. Int Immunopharmacol 30:137–149. https://doi.org/10.1016/j.intimp.2015.11.037
Ramirez-Acuña JM, Cardenas-Cadena SA, Marquez-Salas PA et al (2019) Diabetic foot ulcers: current advances in antimicrobial therapies and emerging treatments. Antibiotics 8:1–32. https://doi.org/10.3390/antibiotics8040193
Rangra NK, Subir Samanta KKP (2021) Evaluation of *Acacia auriculiformis* Benth. Leaves for wound healing activity in type 2 diabetic rats. Pharmacogn Mag 13(Suppl):129–142. https://doi.org/10.4103/pm.pm_496_20
Ranjbar-Heidari A, Khaiatzadeh J, Mahdavi-Shahri N, Tehranipoor M (2012) The effect of fruit pod powder and aquatic extract of *Prosopis farcta* on healing cutaneous wounds in diabetic rat. Zahedan J Res Med Sci 14:16–20
Razzaghi R, Pourbagheri H, Momen-Heravi M et al (2017) The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. J Diabetes Complicat 31:766–772. https://doi.org/10.1016/j.jdiacomp.2016.06.017
Ren J, Yang M, Xu F et al (2019a) Acceleration of wound healing activity with syringic acid in streptozotocin induced diabetic rats. Life Sci 233:116728. https://doi.org/10.1016/j.lfs.2019.116728
Ren S, Chen J, Duscher D et al (2019b) Microvesicles from human adipose stem cells promote wound healing by optimizing cellular functions via AKT and ERK signaling pathways. Stem Cell Res Ther 10:1–14. https://doi.org/10.1186/s13287-019-1152-x
Ren J, Yang M, Chen J et al (2020) Anti-inflammatory and wound healing potential of kirenol in diabetic rats through the suppression of inflammatory markers and matrix metalloproteinase expressions. Biomed Pharmacother 129:110475. https://doi.org/10.1016/j.biopha.2020.110475
Ren S, Guo S, Yang L, Wang C (2022) Effect of composite biodegradable biomaterials on wound healing in diabetes. Front Bioeng Biotechnol 10:1–28. https://doi.org/10.3389/fbioe.2022.1060026
Res M, I-iii W (2011) Polyherbal formulation as a therapeutic option to improve wound healing in the diabetic foot. Indian J Med Res 134:146–147
Rezvani Ghomi E, Khalili S, Nouri Khorasani S et al (2019) Wound dressings: current advances and future directions. J Appl Polym Sci 136:1–12. https://doi.org/10.1002/app.47738

Ribeiro MP, Espiga A, Silva D et al (2009) Development of a new chitosan hydrogel for wound dressing. Wound Repair Regen 17:817–824. https://doi.org/10.1111/j.1524-475X.2009.00538.x

Roberts AB (1995) Transforming growth factor-β: activity and efficacy in animal models of wound healing. Wound Repair Regen 3:408–418. https://doi.org/10.1046/j.1524-475X.1995.30405.x

Rohmayanti R, Hapsari WS (2021) In vivo study of *Centella asiatica* (L.) Urban as a drug gel for diabetes wounds. Medisains 19:77. https://doi.org/10.30595/medisains.v19i3.12274

Romero-Cerecero O, Zamilpa A, Díaz-García ER, Tortoriello J (2014) Pharmacological effect of *Ageratina pichinchensis* on wound healing in diabetic rats and genotoxicity evaluation. J Ethnopharmacol 156:222–227. https://doi.org/10.1016/j.jep.2014.09.002

Romero-Cerecero O, Zamilpa A, Tortoriello J (2015) Effectiveness and tolerability of a standardized extract from *Ageratina pichinchensis* in patients with diabetic foot ulcer: a randomized, controlled pilot study. Planta Med 81:272–278. https://doi.org/10.1055/s-0034-1396315

Rozman NAS, Woei Yenn T, Tan WN et al (2018) *Homalomena pineodora*, a novel essential oil bearing plant and its antimicrobial activity against diabetic wound pathogens. J Essent Oil-Bear Plants 21:963–971. https://doi.org/10.1080/0972060X.2018.1526129

Sahakyan G, Vejux A, Sahakyan N (2022) The role of oxidative stress-mediated inflammation in the development of T2DM-induced diabetic nephropathy: possible preventive action of tannins and other oligomeric polyphenols. Molecules. https://doi.org/10.3390/molecules27249035

Salih M, Abdullah A, Aziz S (2020) Effect of hydroalcoholic extract of *Teucrium polium* on the process of wound healing in diabetic rats. Passer 2:37–45. https://doi.org/10.24271/psr.09

Samancıoğlu S, Esen A, Ercan G et al (2016) A new dressing material in diabetic wounds: wound healing activity of oleuropein-rich olive leaf extract in diabetic rats. Gaziantep Med Journa 22:14–21. https://doi.org/10.5578/GMJ.27960

Santema TBK, Poyck PPC, Ubbink DT (2016) Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: highlights of a Cochrane systematic review. Wound Repair Regen 24:737–744. https://doi.org/10.1111/wrr.12434

Sarandy MM, Novaes RD, Xavier AA et al (2017) Hydroethanolic extract of *Strychnos pseudoquina* accelerates skin wound healing by modulating the oxidative status and microstructural reorganization of scar tissue in experimental type I diabetes. Biomed Res Int. https://doi.org/10.1155/2017/9538351

Scappaticci RAF, Berretta AA, Torres EC et al (2021) Green and chemical silver nanoparticles and pomegranate formulations to heal infected wounds in diabetic rats. Antibiotics. https://doi.org/10.3390/antibiotics10111343

Schindl M, Kerschan K, Schindl A et al (1999) Induction of complete wound healing in recalcitrant ulcers by low- intensity laser irradiation depends on ulcer cause and size. Photodermatol Photoimmunol Photomed 15:18–21. https://doi.org/10.1111/j.1600-0781.1999.tb00047.x

Schürmann C, Goren I, Linke A et al (2014) Deregulated unfolded protein response in chronic wounds of diabetic ob/ob mice: a potential connection to inflammatory and angiogenic disorders in diabetes-impaired wound healing. Biochem Biophys Res Commun 446:195–200. https://doi.org/10.1016/j.bbrc.2014.02.085

Sen S, Basak P, Prasad Sinha B et al (2020) Anti-inflammatory effect of epidermal growth factor conjugated silk fibroin immobilized polyurethane ameliorates diabetic burn wound healing. Int J Biol Macromol 143:1009–1032. https://doi.org/10.1016/j.ijbiomac.2019.09.219

Setyawati A, Wahyuningsih MSH, Nugrahaningsih DAA et al (2021) *Piper crocatum* Ruiz & Pav. ameliorates wound healing through p53, E-cadherin and SOD1 pathways on wounded hyperglycemia fibroblasts. Saudi J Biol Sci 28:7257–7268. https://doi.org/10.1016/j.sjbs.2021.08.039

Shahouzehi B, Shabani M, Shahrokhi N, Sadeghiyan S (2018) Effects of *Pistacia atlantica* resin oil on the level of VEGF, hydroxyproline, antioxidant and wound healing activity in STZ-induced diabetic rats. Ukr Biochem J 90:34–41

Shao Y, Dang M, Lin Y, Xue F (2019) Evaluation of wound healing activity of plumbagin in diabetic rats. Life Sci 231:116422. https://doi.org/10.1016/j.lfs.2019.04.048

Sharma A, Khanna S, Kaur G, Singh I (2021a) Medicinal plants and their components for wound healing applications. Futur J Pharm Sci. https://doi.org/10.1186/s43094-021-00202-w

Sharma R, Sharma SK, Mudgal SK et al (2021b) Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of controlled clinical trials. Sci Rep 11:1–12. https://doi.org/10.1038/s41598-021-81886-1

Sharma P, Navneet, Kaushal A (2022) Green nanoparticle formation toward wound healing, and its application in drug delivery approaches. Eur J Med Chem Rep 6:100088. https://doi.org/10.1016/j.ejmcr.2022.100088

Sharmeen S, Rahman MS, Islam MM et al (2019) Application of polysaccharides in enzyme immobilization. Elsevier

Shi L, Jiang Z, Li J et al (2022a) Metformin improves burn wound healing by modulating microenvironmental fibroblasts and macrophages. Cells 11:1–24. https://doi.org/10.3390/cells11244094

Shi R, Jin Y, Zhao S et al (2022b) Hypoxic ADSC-derived exosomes enhance wound healing in diabetic mice via delivery of circ-Snhg11 and induction of M2-like macrophage polarization. Biomed Pharmacother 153:113463. https://doi.org/10.1016/j.biopha.2022.113463

Siavash M, Shokri S, Haghighi S et al (2015) The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. Int Wound J 12:137–142. https://doi.org/10.1111/iwj.12063

Silva ACC, Eugênio AN, Mariano SS et al (2021) Topical application of *Azadirachta indica* improves epidermal wound healing in hyperglycemic rats. Comp Clin Path 30:461–472. https://doi.org/10.1007/s00580-021-03240-1

Singh S, Gupta B (2017) Choices and challenges of antibiotics therapy in diabetic foot infection. Indian J Endocrinol Metab 21:647–648. https://doi.org/10.4103/ijem.IJEM_481_17

Singh A, Bajpai S, Singh N et al (2014a) Wound healing activity of standardized extract of *Curculigo orchioides* in streptozotocin-induced diabetic mice. Asian Pac J Trop Dis. https://doi.org/10.1016/S2222-1808(14)60414-X

Singh A, Singh PK, Singh RK (2014b) Antidiabetic and Wound healing activity of *Catharanthus roseus* L. in streptozotocin-induced diabetic mice. Am J Phytomed Clin Ther 2:686–692

Singh A, Srivastav R, Pandey A (2017) Protective role of *Terminalia chebula* in streptozotocin-induced diabetic mice for wound healing activity. Br J Med Med Res 22:1–8. https://doi.org/10.9734/bjmmr/2017/33137

Singh MP, Gupta A, Sisodia SS (2020) Wound healing activity of *Terminalia bellerica* Roxb. and gallic acid in experimentally induced diabetic animals. J Complement Integr Med 17:1–10. https://doi.org/10.1515/jcim-2019-0133

Singh WR, Sharma A, Devi HS et al (2022) Icariin improves cutaneous wound healing in streptozotocin-induced diabetic rats. J Tissue Viability 31:197–206. https://doi.org/10.1016/j.jtv.2021.09.004

Singh SK, Dwivedi SD, Yadav K et al (2023) Novel biotherapeutics targeting biomolecular and cellular approaches in diabetic wound

healing. Biomedicines 11:1–34. https://doi.org/10.3390/biomedicines11020613
Singla R, Soni S, Patial V et al (2017a) Cytocompatible anti-microbial dressings of *Syzygium cumini* cellulose nanocrystals decorated with silver nanoparticles accelerate acute and diabetic wound healing. Sci Rep 7:1–13. https://doi.org/10.1038/s41598-017-08897-9
Singla R, Soni S, Patial V et al (2017b) In vivo diabetic wound healing potential of nanobiocomposites containing bamboo cellulose nanocrystals impregnated with silver nanoparticles. Int J Biol Macromol 105:45–55. https://doi.org/10.1016/j.ijbiomac.2017.06.109
Soares RDF, Campos MGN, Ribeiro GP et al (2020) Development of a chitosan hydrogel containing flavonoids extracted from *Passiflora edulis* leaves and the evaluation of its antioxidant and wound healing properties for the treatment of skin lesions in diabetic mice. J Biomed Mater Res - Part A 108:654–662. https://doi.org/10.1002/jbm.a.36845
Soni R, Mehta NM, Srivastava DN (2013) Effect of ethanolic extract of *Cinnamomum tamala* leaves on wound healing in STZ induced diabetes in rats. Asian J Pharm Clin Res 6:39–42
Sovia E (2021) Effect of sweet orange and pomegranate peel extract combination on in vivo antidiabetic and wound healing activity. 37:49–53
Spampinato SF, Caruso GI, De Pasquale R et al (2020) The treatment of impaired wound healing in diabetes: looking among old drugs. Pharmaceuticals 13:1–17. https://doi.org/10.3390/ph13040060
Steffy K, Shanthi G, Maroky AS, Selvakumar S (2018) Enhanced antibacterial effects of green synthesized ZnO NPs using *Aristolochia indica* against multi-drug resistant bacterial pathogens from diabetic foot ulcer. J Infect Public Health 11:463–471. https://doi.org/10.1016/j.jiph.2017.10.006
Steinberg JS, Edmonds M, Hurley DP, King WN (2010) Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. J Am Podiatr Med Assoc 100:73–77. https://doi.org/10.7547/1000073
Sumantri IB, Ismayadi, Mustanti LF (2021) The potency of wound healing of nanogel-containing *Mikania micrantha* leaves extract in hyperglycemic rats. Pharm Nanotechnol 9:339–346. https://doi.org/10.2174/2211738509666211209164105
Suresh TC, Poonguzhali TV, Anuradha V et al (2021) Aqueous extract of *Turbinaria conoides* (j.agardh) kutzing mediated fabrication of silver nanoparticles used against bacteria associated with diabetic foot ulcer. Mater Today Proc 43:3038–3043. https://doi.org/10.1016/j.matpr.2021.01.376
Sutthammikorn N, Supajatura V, Yue H et al (2021) Topical gynura procumbens as a novel therapeutic improves wound healing in diabetic mice. Plants 10:1–19. https://doi.org/10.3390/plants10061122
Takeuchi T, Ito M, Yamaguchi S et al (2020) Hydrocolloid dressing improves wound healing by increasing M2 macrophage polarization in mice with diabetes. Nagoya J Med Sci 82:487–498. https://doi.org/10.18999/nagjms.82.3.487
Talukdar N, Das K, Barman I (2021) A review on ethanobotanical survey of medicinal plants available in North-East India against microbes involved in diabetic foot ulcer. J Diabetol 12:128. https://doi.org/10.4103/jod.jod_45_20
Tan WS, Arulselvan P, Ng S et al (2019) Improvement of diabetic wound healing by topical application of Vicenin-2 hydrocolloid film on Sprague Dawley rats. BMC Complement Altern Med 19:20
Tellechea A, Silva EA, Min J et al (2015) Alginate and DNA gels are suitable delivery systems for diabetic wound healing. Int J Low Extrem Wounds 14:146–153. https://doi.org/10.1177/1534734615580018
Thanganadar Appapalam S, Paul B, Arockiasamy S, Panchamoorthy R (2020) Phytofabricated silver nanoparticles: discovery of antibacterial targets against diabetic foot ulcer derived resistant bacterial isolates. Mater Sci Eng C 117:111256. https://doi.org/10.1016/j.msec.2020.111256
Tonaco LAB, Gomes FL, Velasquez-Melendez G et al (2018) The proteolytic fraction from Latex of Vasconcellea cundinamarcensis (P1G10) enhances wound healing of diabetic foot ulcers: a double-blind randomized pilot study. Adv Ther 35:494–502. https://doi.org/10.1007/s12325-018-0684-2
Tsala D, Joseph M, Simplice T et al (2015) Effect of a methanol extract of *Allium cepa* Linn. on incisional wound healing in alloxan-induced diabetic mice. Appl Med Res 1:90. https://doi.org/10.5455/amr.20150427021827
Tsuboi R, Rifkin DB (1990) Recombinant basic fibroblast growth factor stimulates wound healing in healing-impaired db/db mice. J Exp Med 172:245–251. https://doi.org/10.1084/jem.172.1.245
Tuhin RH, Begum M, Rahman S et al (2017) Wound healing effect of *Euphorbia hirta* linn. (Euphorbiaceae) in alloxan induced diabetic rats. BMC Complement Altern Med 17:1–14. https://doi.org/10.1186/s12906-017-1930-x
van Netten JJ, Lazzarini PA, Armstrong DG et al (2018) Diabetic Foot Australia guideline on footwear for people with diabetes. J Foot Ankle Res 11:1–14. https://doi.org/10.1186/s13047-017-0244-z
Vatankhah N, Jahangiri Y, Landry GJ et al (2017) Effect of systemic insulin treatment on diabetic wound healing. Wound Repair Regen 25:288–291. https://doi.org/10.1111/wrr.12514
Vedha Vijaya T, Srinivasan D, Sengottuvelu S (2013) Wound healing potential of *Melia azedarach* L. leaves in alloxan induced diabetic rats. J Biol Environ Sci 7:265–271
Veeraraghavan VP, Periadurai ND, Karunakaran T et al (2021) Green synthesis of silver nanoparticles from aqueous extract of *Scutellaria barbata* and coating on the cotton fabric for antimicrobial applications and wound healing activity in fibroblast cells (L929). Saudi J Biol Sci 28:3633–3640. https://doi.org/10.1016/j.sjbs.2021.05.007
Verkleij CJN, Roelofs JJTH, Havik SR et al (2010) The role of thrombin-activatable fibrinolysis inhibitor in diabetic wound healing. Thromb Res 126:442–446. https://doi.org/10.1016/j.thromres.2010.08.008
Veves A, Giurini JM, LoGerfo FW (2012) Physiology and pathophysiology of wound healing in diabetes. Diabet Foot Med Surg Manag Third Ed. https://doi.org/10.1007/978-1-61779-791-0
Vijayakumar V, Samal SK, Mohanty S, Nayak SK (2019) Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management. Int J Biol Macromol 122:137–148. https://doi.org/10.1016/j.ijbiomac.2018.10.120
Vitale S, Colanero S, Placidi M et al (2022) Phytochemistry and biological activity of medicinal plants in wound healing: an overview of current research. Molecules 27:3566. https://doi.org/10.3390/molecules27113566
Wackenfors A, Gustafsson R, Sjögren J et al (2005) Blood flow responses in the peristernal thoracic wall during vacuum-assisted closure therapy. Ann Thorac Surg 79:1724–1730. https://doi.org/10.1016/j.athoracsur.2004.10.053
Wang AY, Cao H, Wang L (2019) The effects of Chinese herbal medicines for treating diabetic foot ulcers: a systematic review of 49 randomized controlled trials. Complement Ther Med. https://doi.org/10.1016/j.ctim.2019.03.007
Wang H, Xu Z, Zhao M et al (2021a) Advances of hydrogel dressings in diabetic wounds. Biomater Sci 9:1530–1546. https://doi.org/10.1039/d0bm01747g
Wang XF, Li ML, Fang QQ et al (2021b) Flexible electrical stimulation device with Chitosan-Vaseline® dressing accelerates wound healing in diabetes. Bioact Mater 6:230–243. https://doi.org/10.1016/j.bioactmat.2020.08.003

Wang Y, Chen L, Ren D-Y et al (2022) Mussel-inspired collagen-hyaluronic acid composite scaffold with excellent antioxidant properties and sustained release of a growth factor for enhancing diabetic wound healing. Mater Today Bio 15:100320. https://doi.org/10.1016/j.mtbio.2022.100320

Wang Q, Luo Z, Wu Y-L, Li Z (2023) Recent advances in enzyme-based biomaterials toward diabetic wound healing. Adv Nano-Biomed Res 3:2200110. https://doi.org/10.1002/anbr.202200110

Werner S, Breeden M, Hübner G et al (1994) Induction of keratinocyte growth factor expression is reduced and delayed during wound healing in the genetically diabetic mouse. J Invest Dermatol 103:469–473. https://doi.org/10.1111/1523-1747.ep12395564

Wong A, Chew A, Wang CM et al (2014) The use of a specialised amino acid mixture for pressure ulcers: a placebo-controlled trial. J Wound Care 23:259–269. https://doi.org/10.12968/jowc.2014.23.5.259

World Health Organization (2013) Facts and figures about diabetes. WHO

World Health Organization (2014) Facts and figures about diabetes. WHO

Wu Z, Zheng X, Gong M, Li Y (2016) Myricetin, a potent natural agent for treatment of diabetic skin damage by modulating TIMP/MMPs balance and oxidative stress. Oncotarget 7:71754–71760. https://doi.org/10.18632/oncotarget.12330

Wynn M, Freeman S (2019) The efficacy of negative pressure wound therapy for diabetic foot ulcers: a systematised review. J Tissue Viability 28:152–160. https://doi.org/10.1016/j.jtv.2019.04.001

Xie Z, Paras CB, Weng H et al (2013) Dual growth factor releasing multi-functional nanofibers for wound healing. Acta Materialia Inc

Xiong Y, Chen L, Liu P et al (2022) All-in-one: multifunctional hydrogel accelerates oxidative diabetic wound healing through timed-release of exosome and fibroblast growth factor. Small. https://doi.org/10.1002/smll.202104229

Xu J, Min D, Guo G et al (2018) Experimental study of epidermal growth factor and acidic fibroblast growth factor in the treatment of diabetic foot wounds. Exp Ther Med 15:5365–5370. https://doi.org/10.3892/etm.2018.6131

Yadav JP (2023) Based on clinical research matrix metalloprotease (MMP) inhibitors to promote diabetic wound healing. Horm Metab Res 55:752–757. https://doi.org/10.1055/a-2171-5879

Yadav JP, Grishina M, Shahbaaz M et al (2022a) *Cucumis melo* var. momordica as a potent antidiabetic, antioxidant and possible anticovid alternative: investigation through experimental and computational methods. Chem Biodivers. https://doi.org/10.1002/cbdv.202200200

Yadav JP, Patel DK, Dubey NK et al (2022b) Wound healing and antioxidant potential of *Neolamarckia cadamba* in streptozotocin-nicotinamide induced diabetic rats. Phytomed plus. https://doi.org/10.1016/j.phyplu.2022.100274

Yadav JP, Patel DK, Pathak P, Grishina M (2022c) Role of G-protein coupled receptor (GPCRs)/(GPR-120) as an agonists in diabetic wound healing. Obes Med 36:100466. https://doi.org/10.1016/j.obmed.2022.100466

Yadav JP, Singh AK, Grishina M et al (2022d) *Cucumis melo* Var. agrestis Naudin as a potent antidiabetic: investigation via experimental methods. Phytomed plus 2:100340. https://doi.org/10.1016/j.phyplu.2022.100340

Yadollah-Damavandi S, Chavoshi-Nejad M, Jangholi E et al (2015) Topical hypericum perforatum improves tissue regeneration in full-thickness excisional wounds in diabetic rat model. Evid-Based Complement Altern Med. https://doi.org/10.1155/2015/245328

Yammine K, Assi C (2022) Surgery versus nonsurgical methods in treating neuropathic plantar forefoot ulcers: a meta-analysis of comparative studies. Int J Low Extrem Wounds 21:7–17. https://doi.org/10.1177/1534734620923425

Yang SL, Han R, Liu Y et al (2014) Negative pressure wound therapy is associated with up-regulation of bFGF and ERK1/2 in human diabetic foot wounds. Wound Repair Regen 22:548–554. https://doi.org/10.1111/wrr.12195

Yang P, Pei Q, Yu T et al (2016) Compromised wound healing in ischemic type 2 diabetic rats. PLoS ONE 11:1–19. https://doi.org/10.1371/journal.pone.0152068

Yang P, Wang D, Shi Y et al (2020a) Insulin-containing wound dressing promotes diabetic wound healing through stabilizing HIF-1α. Front Bioeng Biotechnol 8:1–10. https://doi.org/10.3389/fbioe.2020.592833

Yang Q, Zhang Y, Yin H, Lu Y (2020b) Topical recombinant human epidermal growth factor for diabetic foot ulcers: a metaanalysis of randomized controlled clinical trials. Elsevier

Yarahmadi A, Saeed Modaghegh MH, Mostafavi-Pour Z et al (2021) The effect of platelet-rich plasma-fibrin glue dressing in combination with oral vitamin E and C for treatment of non-healing diabetic foot ulcers: a randomized, double-blind, parallel-group, clinical trial. Expert Opin Biol Ther 21:687–696. https://doi.org/10.1080/14712598.2021.1897100

Zadeh MAA et al (2020) Evaluation of beneficial influence of local application of *Crocus pallasii* subsp. Haussknechtii Boiss. Extract on healing of full thickness excisional infected wounds in diabetic rats. Bull Emerg Trauma 8:169–178. https://doi.org/10.30476/BEAT.2020.82567.Journal

Zenão S, Aires A, Dias C et al (2017) Antibacterial potential of *Urtica dioica* and *Lavandula angustifolia* extracts against methicillin resistant *Staphylococcus aureus* isolated from diabetic foot ulcers. J Herb Med 10:53–58. https://doi.org/10.1016/j.hermed.2017.05.003

Zeng Z, Zhu BH (2014) Arnebin-1 promotes the angiogenesis of human umbilical vein endothelial cells and accelerates the wound healing process in diabetic rats. J Ethnopharmacol 154:653–662. https://doi.org/10.1016/j.jep.2014.04.038

Zhang EY, Gao B, Shi HL et al (2017a) 20(S)-protopanaxadiol enhances angiogenesis via HIF-1α-mediated VEGF secretion by activating p70S6 kinase and benefits wound healing in genetically diabetic mice. Exp Mol Med 49:1–12. https://doi.org/10.1038/emm.2017.151

Zhang P, Lu J, Jing Y et al (2017b) Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis†. Ann Med 49:106–116. https://doi.org/10.1080/07853890.2016.1231932

Zhao R, Liang H, Clarke E et al (2016) Inflammation in chronic wounds. Int J Mol Sci 17:1–14. https://doi.org/10.3390/ijms17122085

Zheng Y, Du X, Yin L, Liu H (2022) Effect of electrical stimulation on patients with diabetes-related ulcers: a systematic review and meta-analysis. BMC Endocr Disord 22:1–9. https://doi.org/10.1186/s12902-022-01029-z

Zhou K, Ma Y, Brogan MS (2015) Chronic and non-healing wounds: the story of vascular endothelial growth factor. Med Hypotheses 85:399–404. https://doi.org/10.1016/j.mehy.2015.06.017

Zhou J, Wei T, He Z (2021a) ADSCs enhance VEGFR3-mediated lymphangiogenesis via METTL3-mediated VEGF-C m6A modification to improve wound healing of diabetic foot ulcers. Mol Med. https://doi.org/10.1186/s10020-021-00406-z

Zhou R, Xiang C, Cao G et al (2021b) Berberine accelerated wound healing by restoring TrxR1/JNK in diabetes. Clin Sci 135:8–11. https://doi.org/10.1042/CS20201145

Zhu J, Jiang G, Hong W et al (2020) Rapid gelation of oxidized hyaluronic acid and succinyl chitosan for integration with insulin-loaded micelles and epidermal growth factor on diabetic wound

healing. Mater Sci Eng C 117:111273. https://doi.org/10.1016/j.msec.2020.111273
Zubair M, Ahmad J (2019) Role of growth factors and cytokines in diabetic foot ulcer healing: a detailed review. Rev Endocr Metab Disord. https://doi.org/10.1007/s11154-019-09492-1
Zuber M, Rajesh V, Anusha K et al (2013) Wound healing activity of ethanolic extract of *Allium sativum* on Alloxan induced diabetic rats family (Liliaceae). Int J Sci Invent Today 2:40–57

Authors and Affiliations

Jagat Pal Yadav[1,2,3] · Ankit Kumar Singh[5] · Maria Grishina[6] · Prateek Pathak[7] · Amita Verma[3] · Vikas Kumar[4] · Pradeep Kumar[5] · Dinesh Kumar Patel[1]

✉ Jagat Pal Yadav
j.p.yaduvansi@gmail.com; 19phpsc210@shiats.edu.in

✉ Dinesh Kumar Patel
dkp.itbhu@gmail.com; dinesh.patel@shiats.edu.in

1 Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj 211007, India

2 Pharmacology Research Laboratory, Faculty of Pharmaceutical Sciences, Rama University, Kanpur 209217, India

3 Bioorganic and Medicinal Chemistry Research Laboratory, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj 211007, India

4 Natural Product Drug Discovery Laboratory, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj 211007, India

5 Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Bathinda 151401, India

6 Laboratory of Computational Modeling of Drugs, Higher Medical and Biological School, South Ural State University, Chelyabinsk 454008, Russia

7 Department of Pharmaceutical Analysis, Quality Assurance, and Pharmaceutical Chemistry, School of Pharmacy, GITAM (Deemed to Be University), Hyderabad 502329, India