Evolving spectrum of diabetic wound: Mechanistic insights and therapeutic targets

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Abstract

Diabetes mellitus is a chronic metabolic disorder resulting in an increased blood glucose level and prolonged hyperglycemia, causes long term health consequences. Chronic wound is frequently occurring in diabetes patients due to compromised wound healing capability. Management of wounds in diabetic patients remains a clinical challenge despite many advancements in the field of science and technology. Increasing evidence indicates that alteration of the biochemical milieu resulting from alteration in inflammatory cytokines and matrix metalloproteinase, decrease in fibroblast and keratinocyte functioning, neuropathy, altered leukocyte functioning, infection, *etc.*, plays a significant role in impaired wound healing in diabetic people. Apart from the current pharmacotherapy, different other approaches like the use of conventional drugs, antidiabetic medication, antibiotics, debridement, offloading, platelet-rich plasma, growth factor, oxygen therapy, negative pressure wound therapy, low-level laser, extracorporeal shock wave bioengineered substitute can be considered in the management of diabetic wounds. Drugs/therapeutic strategy that induce angiogenesis and collagen synthesis, inhibition of MMPs, reduction of oxidative stress, controlling hyperglycemia, increase growth factors, regulate inflammatory cytokines, cause NO induction, induce fibroblast and keratinocyte proliferation, control microbial infections are considered important in controlling diabetic wound. Further, medicinal plants and/or phytoconstituents also offer a viable alternative in the treatment of diabetic wound. The focus of the present review is to highlight the molecular and cellular mechanisms, and discuss the drug targets and treatment strategies involved in the diabetic wound.

Core Tip: This paper reviewed molecular pathways and epigenetic mechanisms involved in the pathogenesis of diabetic wounds. The role of microbiota, oxidative stress, inflammatory cytokines, and alteration in the factors involved in normal wound healing process was highlighted. Molecular targets of therapeutic agents, the role of phytochemicals was discussed. The efficacy of several pharmacotherapy, treatment strategies, and recent clinical trials aiming to improve the outcome of diabetic foot ulcers was reviewed.

INTRODUCTION

The process of wound healing is complex and requires spatial as well as temporal synchronization between different types of cells with specific functions. Hemostasis, inflammatory phase, proliferative phase, re-epithelialization, and remodelling phase are the four major phases of wound healing process, which result in the restoration of functional integrity of tissues[1-3]. Alteration in the microenvironment due to diabetes mellitus (DM) results in a change in the level of oxygen, chemokines, synthesis of growth factors, extracellular matrix, oxidative stress that in turn alter normal cellular recruitment and activation, and induce impaired or delayed wound healing[1,3]. Ageing, genetic disorders, obesity, and metabolic disorders including DM, are responsible for the abnormal wound healing process, that enhances the risk of developing chronic wound[1,3,4]. It was estimated that chronic wounds directly affect the quality of life of about 2.5% population of the United States, and the medicare cost for management of all wounds and the related situation was projected between $28.1 to $96.8 billion[5]. Management of wounds in the diabetic individual is a major clinical and social concern. The hyperglycaemic environment in diabetic people causes impaired and delayed wound healing[4], making the situation more perilous as the number of diabetic people is increasing day by day. It was also found that treatment and management of diabetic ulcers and surgical wounds were the most expensive[5]. The IDF Diabetes Atlas estimated that the prevalence of DM in 2021 was 10.5% (536.6 million people in the 20-79 year age group), which will increase to 12.2% (783.2 million in the 20-79 year age group) by 2045. Global health expenditures related to the management of DM and its complications are expected to reach $966 billion in 2021[6]. It was also predicted that almost half of the adult population (44.7%; 239.7 million of 20-79 years old) were unaware of their diabetic condition. People may develop micro and macrovascular complications during an asymptomatic diabetic state[7]. Impaired or delayed wound healing affects about 25% of diabetic people. A study suggested that 1 in 3 to 1 in 5 diabetic individuals are at risk of chronic non-healing wounds, including diabetic foot (with a very high recurrence rate) in their lifetime[8]. Zhang *et al*[9] estimated that the global prevalence of diabetic foot is 6.3%, which usually affects type 2 diabetic people, older people, and people with a longer duration of DM.

Both the extrinsic and intrinsic factors are responsible for delay in the wound healing process in diabetic patients. Repeated trauma or mechanical stress in the diabetic foot can lead to neuropathy and ischemic situation. Glucose-rich environment results in increased generation of advanced glycation end-products (AGEs) and elevated levels of inflammatory cytokines [*i.e.*, interleukin (IL)-1β and tumor necrosis factor α (TNF-α)] for a persistent period that hinders the normal process of wound healing[10, 11]. In turn, hyperglycemia reduces collagen synthesis, growth factor production, macrophage function, angiogenic response, migration and proliferation of fibroblast and keratinocyte, epidermal nerve count, and the balance between extracellular matrix (ECM) component accumulation and matrix metalloproteinase (MMP) induced remodelling [4,12]. The normal wound healing process and effect of the hyperglycemic condition are depicted in Figure 1.

Despite the presence of protocols to standardize care in the diabetic wounds, as well as numerous advancements in scientific research and in clinical fronts, DM remains a problematic situation for wound healing. This paper is an attempt to highlight the mechanistic insights, plausible therapeutic targets, and pharmacotherapeutic approaches, particularly the role of phytochemicals in the management of diabetic wounds, in light of recent shreds of evidence.
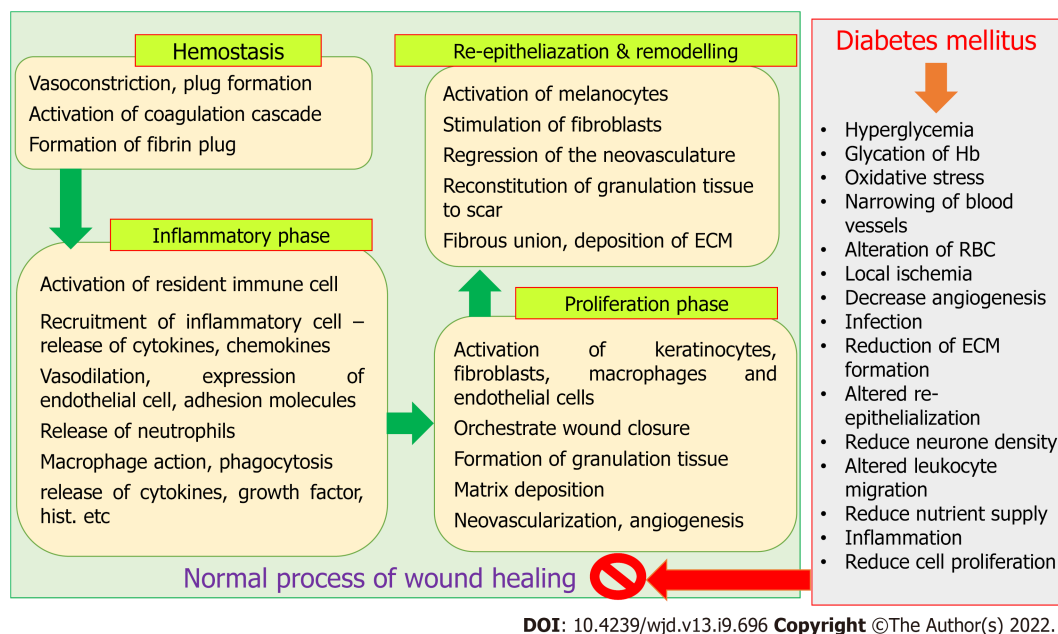
Figure 1 Normal process of wound healing and effect of diabetes mellitus. ECM: Extracellular matrix.

MECHANISTIC INSIGHTS OF DIABETIC WOUND

Wound healing, being an evolutionary conservation process, restores impaired epithelial barriers through a cascade of events including inflammatory responses, proliferation, cellular migration, angiogenesis, and remodeling of tissues[13]. DM interferes with the normal healing process to provoke non-healing wound, and leads to complications including walking difficulty and infections like septicemia, abscess, cellulitis, osteomyelitis, and gangrene[4]. Acute diabetic wounds with an impaired healing process of unknown aetiology are the first signs of chronic diabetic wounds. Hyperglycemia, hypoxia, chronic inflammation, neuropathy, circulatory dysfunctions, alteration in neuropeptide signalling, and infections impede the diabetic wound healing process. Importantly, due to the heterogeneous nature of the diabetic wound, there exist no clear implications from the pathogenic vantage. The following subsections discuss the potential factors underlying the pathogenesis of diabetic wound.

Molecular implications

Impaired wound healing associated with diabetes remains inconclusive. However, the alterations in cellular factors and biochemical mediators have been believed to be involved in the development and progression of diabetic wound (Figure 2). Factors like hyperglycemia and oxidative stress in diabetic patients result in dysregulated macrophage polarization through modulation of epigenetic codes to delay the process of wound healing[14,15]. Hyperglycemia is implicated in impaired wound closure in diabetic foot ulcers (DFUs), with reduced skin cell function and the formation of atherosclerosis and neuropathy as possible contributors[8]. The development of atherosclerosis leads to alteration in the physiology of endothelial cells along with deprivation of nutrients in the wound site, critically affecting the healing process. Patients with type 1 DM are more prone to macrovascular diseases, especially affecting femoral and metatarsal arteries[16,17]. DM associated early microvascular deficiencies include decreased capillary size, basement membrane thickening, and arteriolar hyalinosis. Thickening of the membrane disrupts the physiological exchanges and causes altered leucocyte migration, and thereby increasing the risk of microbial infections[18,19]. Hyperglycemia disrupts protein translation as well as the migration and proliferation of fibroblasts and keratinocytes involved in the process of re-epithelialization[20-22]. For instance, altered expression of proteins like cytoskeletal keratin proteins (K2/K6/K10) associated with keratinocyte differentiation, and LM-3A32, a laminin-5 α3 chain precursor protein that regulates epithelial cell binding to the basement membrane, was reported in subjects with DFUs[23]. As LM-3A32 is required for the survival and differentiation of keratinocytes, reduction in this protein affects the re-epithelialization process[24]. Interestingly, the expression of mRNA and microRNA was found to be non-significant in diabetic and non-diabetic foot skin fibroblasts[25]. However, fibroblasts from DFUs were reported to exhibit altered morphology, growth factor unresponsiveness, ECM deposition, and reduced proliferation and migration[26-29]. Impaired vasculogenesis and angiogenesis due to deregulation of the growth factors and receptors leads to impaired wound healing. Dysfunctional endothelial progenitor cells (EPC) or reduction in their numbers and transition to proinflammatory EPC phenotypes have been implicated in DM[30,31]. Notably, EPC dysfunction and altered recruitment are contributed by hyperglycemia, chronic inflammation, oxidative
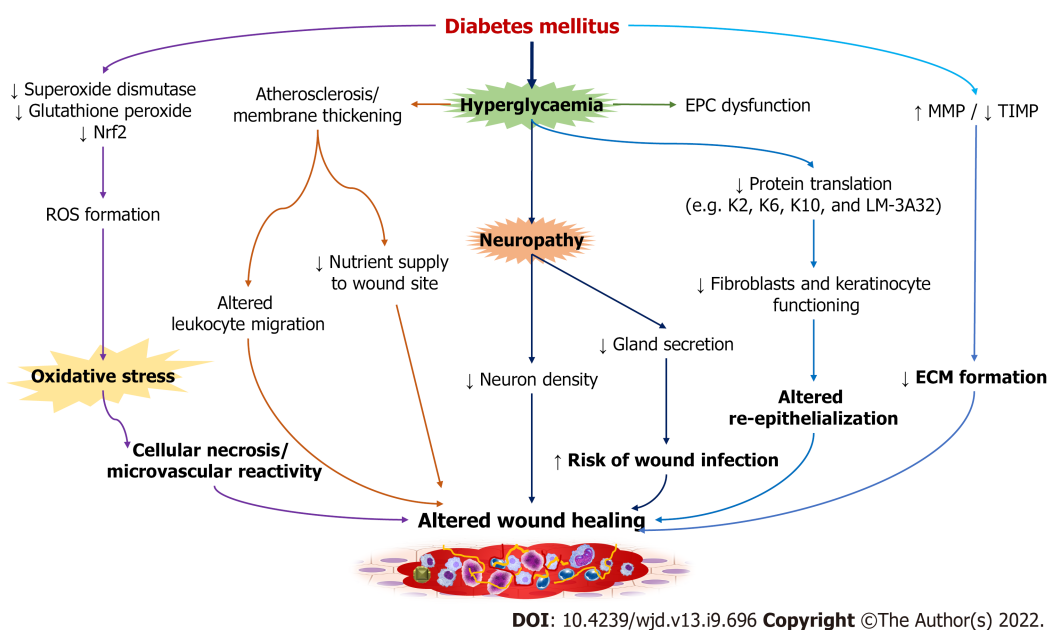
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Figure 2 Altered cellular factors and biochemical mediators involved in the development of diabetic wound. Nrf2: Nuclear factor erythroid factor 2-related factor 2; ROS: Reactive oxygen species; EPC: Endothelial progenitor cell; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase; ECM: Extracellular matrix.

stress, and activation of NADPH oxidase associated with diabetes pathogenesis[32]. Prolonged IL-1β production and reduced expression of peroxisome proliferator-activated receptor-γ are also involved in the impairment of wound healing in DM[33]. Higher expression of MMPs including MMP-1, 2, 8, 9, 14, and 26, and lower expression of their tissue inhibitors were also reported in diabetes[34,35]. In patients with DFUs, it was reported that there is an increase in MMPs and a decrease in tissue inhibitor of metalloproteinase (TIMP)-2, which supports the fact that in a proteolytic environment, diabetic wound fails to heal due to reduction in ECM formation[36]. An increase in MMPs also contributes to matrix degradation, delayed cell migration, and inhibition of collagen deposition[36]. Oxidative stress resulting due to decrease action of enzymes like superoxide dismutase and glutathione peroxidase augment diabetic wound. Overproduction of reactive oxygen species (ROS) from hexosamine, polyol, and AGE pathways affects the later stages of diabetic wound healing, particularly by damaging the peripheral nerves. Consequently, the detrimental effect on the structure, supply, and metabolism of peripheral nerves (neuropathy) increases the risk of DFU development[37]. Hyperglycemia not only contributes to impaired healing but also makes skin prone to injury. Decrease in nuclear factor erythroid factor 2-related factor 2 (Nrf2) in diabetic patients increases the oxidized proteins and ROS generation[38,39]. In Nrf2 knockout mice, delayed wound healing was reported when compared to a Nrf2^{+/+} mice, possibly due to oxidative DNA damage, elevated MMP-9 expression, and lower level of transforming growth factor-beta 1 (TGF-β1) expression[40]. Hyperglycemia also leads to an increase in neutrophil extracellular traps release, which has been implicated in delayed wound healing in both murine and human models[13,41].

The formation of a diabetic wound is also linked to several forms of neuropathy, including sensory, motor, and autonomic. Sensory deficits, for example, cause a loss of protective symptoms, whereas motor neuropathy causes anatomical deformities and ischemic death in the plantar region of the foot [42], and autonomic neuropathy reduces sweat secretion from the glands, making skin dry and increasing the risk of infection and pruritus[43]. Furthermore, neuropathy causes a decrease in neuron density, causing impairment in wound healing. Primarily, diabetic neuropathy occurs in nerves that are dependent on nerve growth factor[8]. Impaired microvascular processes along with autonomic neuropathy and denervation of sympathetic nerves disrupt the blood flow. Cellular necrosis and microvascular reactivity are also triggered by Poly (ADP-ribose) polymerase enzyme *via* oxidative DNA damage[16,44]. In diabetic neuropathy, impairment of C-fibre dependent neurovascular responses leads to abnormality in the release of histamine, substance P, and calcitonin related peptide, thus exhibiting altered vasodilatation in case of stress like pressure or trauma[44]. However, the direct link between neuropathic abnormalities and glucose control is yet to be proven.

Epigenetic mechanisms
Despite the fact that epigenetic pathways have a role in a variety of diabetic complications, evidence of epigenetics in diabetic wound or impaired wound healing is still emerging. The role of microRNA in diabetic wound was first highlighted by a study that revealed up-regulation of miR-503 in plasma

obtained from DFUs and in human umbilical vein endothelial cells (HUVEC). *In vitro* experiment suggested the detrimental effect of forced miR-503 expression on function of HUVEC cells resulting due to impaired migration, proliferation, and formation of blood vessels[45]. Blockage of miR-503 expression showed improvement in angiogenesis in diabetic animals with limb ischemia[45,46]. Another study demonstrated that diabetic mice had a distinct microRNA signature, with differential expression of fourteen microRNAs[47]. Of these, expression of miR-146b was found to be up-regulated by 30 fold. Though miR-21 was up-regulated in diabetic skin, it was reduced in diabetic wound healing. This study suggested the necessity of miR-21 expression for fibroblast migration and miR-21 knock-down results in altered cellular migration. Similarly, another study showed the stabilisation of hypoxia-inducible factor α leads to miR210 expression, which silences the expression of E2F3, an important element of wound healing[46]. This implies the fact that epigenetic changes in miR-210 lead to impaired wound re-epithelialization and reduced proliferation. The involvement of DNA methylation in impaired diabetic wound healing is being studied in many experiments. A study reported inhibition of DNA methyltransferase 1 (DNMT1), an enzyme that transfers a methyl group to the cytosine ring to produce 5-methylcytosine associated with transcriptional repression, suppresses inflammatory signals in bone marrow derived macrophages and also promotes M2-like macrophage formation[48]. This finding was supported by DNMT1 knockdown in db/db mice showing improvement in wound healing[49]. In contrast to that, demethylation of MMP-9 promoter in keratinocytes was reported to be involved in the induction of diabetic wound[50,51]. Apart from the role of DNA methylation in wound healing, it is also associated with metabolic memory, insulin resistance, and other diabetic complications[52,53]. Unlike DNA methylation, histone methylation does not always lead to transcriptional repression. Instead, it silences or promotes transcription based on the target residue and methyl groups. Methylation of histone H3K4 is regulated by SET domain containing protein family, particularly MLL1 that promotes inflammatory gene expression in nuclear factor kappa B-dependent manner[54-56]. A study reported the role of mixed-lineage leukemia-1 (MLL1) is to catalyze H3K4me3 deposition in macrophages during the process of wound healing[57]. Delayed wound healing and reduced pro-inflammatory cytokine generation were reported in a myeloid-specific MLL1 deletion in mice. Monocytes isolated from patients with type-2 DM demonstrated higher MLL1 expression, indicating dynamic regulation of MLL1 expression during diabetic wound healing. In diet-induced obesity model of diabetes, increased expression of histone demethylase (*i.e.*, lysine-specific demethylase 6B or JMJD3) that targets H3K27me3 was seen in wound macrophages[58,59]. Epigenetic regulation of IL-6 expression in neutrophils was believed to be impacted by toll-like receptor (TLR) activation associated with increased H3K27ac, H3K4me3, and acetylated histone H4[60]. Re-epithelialization is also promoted by JMJD3 expression, which induces keratinocyte migration to the wound site[61]. Similar report suggests upregulation of JMJD3 expression on the wound site is necessary for early onset of the wound healing process, which is absent in diabetic wound[62]. However, it will be too oversimplified interpolation as most of these findings are limited to normal wounds; thus, further studies are warranted. Other histone modifications including histone acetylation or deacetylation, histone phosphorylation, histone-arginine demethylation or methylation, and ATP-dependent chromatin remodelling are also being studied for their potential role in diabetic wound healing[62].

Microbiological perspectives

Certainly, pathogenic infections are not directly associated with the pathophysiology of diabetic wounds but are critical from the vantage of impaired wound healing, hospitalization, morbidity, and amputation. However, the role in the initiation of diabetic wound in case of trauma remains unclear. The rapid spreading of infections and high microbial burden exhibit detrimental effect on the wound healing process. Injury to the superficial skin layer allows polymicrobial contamination and colonization, affecting diabetic wound. Particularly, infections like cellulitis, osteomyelitis, and abscesses are of major concern[16]. The advent of high-throughput sequencing technologies like microarray, 16S rRNA sequencing, and whole-genome sequencing have enabled the expansion of diabetic wound microbiome. Diabetic wound has demonstrated higher colonization of *Staphylococcus aureus* and *S. epidermidis*[63]. Another study reported *Staphylococcus*, *Enterobacteriaceae*, and *Pseudomonas* to be the most common colonizers in DFUs[64]. Stratification of DFUs as per infection severity revealed higher bacterial diversity in severely infected DFUs, while *Staphylococcus* and *Streptococcus* were found to be the most abundant in mild-to-moderate DFUs[65]. It was similar to a previous finding that found diverse microbiota (with higher incidence of anaerobic and Proteobacteria infection) in deep chronic ulcers, while *Staphylococcus* was found to be abundant in acute and superficial ulcers[66]. However, contrary to these reports, another study reported *Staphylococcus* spp. to be the primary culture detected in the microbiome in diabetic foot osteomyelitis[67]. A higher prevalence of *S. aureus* colonization in DFUs and intact diabetic skin lead to systemic infection and osteomyelitis[63]. Indeed, in a Nigerian observational multi-center study, it was reported that the presence of osteomyelitis is an important predictor of wound healing in hospitalized patients with DFUs[68]. The expression of proteolytic factors by *Streptococcus* and *Staphylococcus* are believed to be the disruptor of skin barrier. For example, SpeB released by *Streptococcus* leads to cleavage of desmoglein 1 and 3 that causes epidermal barrier damage [69]. The alkaline environment of DFUs contributes to the formation of bacterial biofilm, leading to complex host–microbiome interaction[70]. The formation of bacterial biofilm along with alkaline pH

affects drug action and is responsible for antibiotic resistance[71]. One should appreciate various other factors influencing this intricate microbiome network and its potential correlation with clinical significance. Keeping all this evidence in sight, more longitudinal studies are anticipated for an adequate understanding of the probable relevance of the microbiome to clinical outcomes.

PLAUSIBLE DRUG TARGETS

In recent studies, neuropathy, peripheral vascular disease, and impaired wound healing have all been identified as key contributors to diabetic wounds and have all become critical targets in improving wound healing in diabetic patients. But despite of this well-established knowledge, comparatively fewer treatment options are being implemented in routine practice. The expression of cellular components of participating cells, as well as cytokines, growth factors, and other molecular factors required for coordinating the normal healing process, is impaired in diabetic wounds, and as a result, they are unable to progress in synchrony and are primarily checked in the inflammatory phase. Therapeutic strategy targeting such cellular and molecular pathway could be useful for effective management of diabetic wound.

As a result of elevated blood sugar levels in diabetic conditions, damage to nerve fiber occurs, leading to diabetic neuropathy, which can be sensory, motor or autonomic[72]. Sensory neuropathy can result in one of two outcomes: a painful foot or a foot that is devoid of sensation[12]. Motor neuropathy is accompanied by muscle weakening, atrophy, and paresis. The inability of an intrinsic muscle to keep the foot in its normal state resulting because of weakening of inter-osseous muscles in the foot, which contributes to foot deformity. When the foot deforms, the pressure distribution throughout the foot changes, and aberrant pressure develops at various locations on the foot[73]. Keratosis and callus development occur as a result of repeated pressure, which leads to damage to callused areas and induces ulcer formation beneath the callus that further causes cracks on the foot[74-77]. Malfunctioning of the sympathetic nerves supplying the sweat glands in the foot reduces the sweat and moisture in the feet, which leads to the development of cracks[78]. Inflammation, necrosis, and ulceration result when an unnoticed injury is combined[16,79]. Currently, duloxetine, anticonvulsant pregabalin and opioid tapentadol are being prescribed for diabetic peripheral neuropathy. Besides these, a substance like α-lipoic acid has shown effectiveness in delaying or reversing peripheral diabetic neuropathy through its multiple antioxidant properties[80]. Neuropeptides such as substance-P and neuropeptide-Y are also been found to be effective in diabetic neuropathy and associated wound[81,82].

Peripheral vascular dysfunction is another major cause of diabetic wound in a majority of diabetic patients. The wound healing process in the diabetic condition is hampered by the altered physiological response due to glycation of hemoglobin, alteration of the red blood cell membrane and narrowing of blood vessels which cause the decreased supply of nutrients and oxygen to tissues[12]. The development of atherosclerotic plaque in diabetic patients also leads to the development of non-healing wound. Therefore, pharmacotherapeutic agents like antioxidant phytochemicals that can avert oxidative stress and formation of AGEs could be useful in treating diabetic wound.

Bacterial infection is one of the most common causes of wounds, and diabetic individuals are more vulnerable to it because of delayed wound healing and immunosuppression[83,84]. The biofilms created by microorganisms protect them from antimicrobial agents and the immune system while also interfering with the healing process, which is one of the most prevalent reasons for amputation of lower limbs in diabetic wounds[14]. Therefore, empiric therapy should include broad-spectrum antibiotics. In recent times, drug resistance is a bigger problem and several drugs are in use in the treatment of DFU.

Neutrophils, monocytes, macrophages, keratinocytes, fibroblasts, T cells, B cells, mast cells, and endothelial cells are all involved in wound healing and are responsible for the formation and modulation of pro-inflammatory cytokines and growth factors such IL-1, TNF-α, IL-6, vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and TGF-β. Hyperglycemia and oxidative stress lead to dis-regulation of these cells, resulting in delayed wound healing[85-87]. Increased amounts of pro-inflammatory cytokines cause an inflammatory cascade to be disrupted, resulting in hyper-inflammation and insulin resistance. These also lead to reduced angiogenesis and microvascular issues, impaired macrophage and neutrophil function, impaired keratinocyte and fibroblast migration and proliferation, and impaired growth factor generation[15,88-90]. Many of these cells play a vital role in the immune response, which is also important for wound healing. Various chemokines whose expression can regulate the function of immune cells have the potential to enhance wound healing. Mast cells with close coordination with macrophages, endothelial cells, and fibroblasts, play a key role in matrix remodeling and disrupt the balance of pro- and anti-angiogenic molecules in wound tissues, affecting angiogenesis and vascular regression in the proliferative and remodeling phases, respectively[91-93]. As a result, mast cell degranulation inhibitors such as disodium cromoglycate, quercetin, and luteolin may be promising options for improving diabetic wound healing [92]. Heat shock proteins (HSPs) aid wound healing by attracting dermal fibroblasts, stimulating cell proliferation and keratinocyte differentiation, reducing oxidative stress, ameliorating actin microfilaments, aiding endothelial cell migration, and enhancing pro-collagen synthesis and protein

homeostasis[94,95]. Reduced levels of HSPs and their downstream components TLR4 and p38-MAPK (mitogen-activated protein kinases) in diabetic patients are responsible for the slowed healing process [96]. Therefore, targeting this as a therapeutic target could be useful in diabetic wound conditions.

Growth factors are biologically active polypeptides that play an important role in the onset and maintenance of wound healing[97]. In diabetics, any change, *i.e.*, down-regulation of growth factor receptors and rapid degradation of growth factors, causes wound healing to be delayed. Factors such as VEGF, IGF, TGF-β, KGF24, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), TNF-α, and IL-6 are significantly reduced in diabetes patients, and several of them have been demonstrated to significantly enhance wound healing in many studies. Growth factors that cause a molecular alteration in the wound micro-environment may help patients with non-responsive wounds. PDGF is a major serum mitogen that promotes fibroblast proliferation, matrix formation, and connective tissue maturation[98]. They attract fibroblasts and inflammatory cells and aid in the production of glycosaminoglycans, proteoglycans, and collagen. During the healing process, it is a critical mediator in fibroblast migration and proliferation, the formation of granulation tissue proteins and provisional extracellular matrix, and angiogenesis[99]. The expression of PDGF and its receptors is reduced in diabetic wounds, and many clinical studies employing PDGF have shown improved healing time[100,101]. It is indicated for the treatment of infections that have spread to deeper subcutaneous tissues or beyond areas with a sufficient blood supply[102]. Another growth factor, bFGF, has a stimulatory effect on fibroblast growth and differentiation, as well as the proliferation of vascular smooth muscle cells, endothelial cells, ECM metabolism, growth, and movement of mesodermally derived cells, all of which speed up the formation of granulation tissue and promote wound healing [103]. Angiogenesis, cell proliferation, migration, differentiation, neo-vascularization, re-epithelialization, and collagen disposition were all stimulated by the clinical application of bFGF, all of which contribute to wound healing[104]. It promotes mesodermal cell chemotaxis and extracellular matrix growth and expedites both acute and chronic wound healing, which gives a scar-free cure[105]. VEGF is a potent angiogenic cytokine that has a substantial impact on healing and promotes rate-limiting processes in vasculogenesis and angiogenesis[106]. Low VEGF levels cause impaired wound healing and aberrant VEGF receptor patterns in diabetics. Decreased VEGF mRNA levels, increased VEGF receptor (VEGFR)-1 Levels, and decreased VEGFR-2 Level are some of the key causes of wound non-healing[107]. In diabetic wounds, VEGF leads to an increase in capillary density, which enhances blood perfusion and metabolism in the wounded tissue[108]. VEGF causes an increase in capillary density, which improves blood perfusion and metabolism in the wounded tissue. This leads to the facilitation of the supply of oxygen and nutrients to assist the growth and function of reparative cells. It is the primary regulator of wound revascularization and permeability and participates in the formation of granulation tissue. On binding with the EGF receptors, EGF causes an increase in epidermal cell, cell motility, cellular migration, mesenchymal regeneration, angiogenesis and cell proliferation[109]. Application of EGF into the wound site results in a greater pharmacodynamic response in terms of granulation tissue growth and wound closure. IGF-1 promotes wound healing by assisting in cell granulation and re-epithelisation, promoting endothelial cell chemotaxis and keratinocyte and fibroblast proliferation, while lower levels of both IGF-1 and TGF-β in wound tissue cause wound healing to be delayed[110, 111]. TGF-β attracts and stimulates inflammatory cells such as neutrophils, macrophages, lymphocytes, keratinocytes, and fibroblasts, as well as the synthesis of growth factors, which speed up vascularisation, angiogenesis, and ECM synthesis while slowing down ECM degradation[112]. Therapeutic agents or strategy, which can ameliorate this positively, are useful in diabetic wound condition. Several drugs and phytoconstituents have shown their positive effect in diabetic wounds targeting these biomolecules. The use of platelet-rich plasma (PRP), EGF, PDGF, and FGF has shown promising effects in the treatment of diabetic wound in a better way.

MMPs are a class of endopeptidase that play a key part in wound debridement, as well as angiogenesis, epithelialization, and extracellular matrix remodeling[113]. Matrix proteins such as collagens, basement membrane collagens, proteoglycans, elastin, and fibronectin are digested by the MMPs. TIMPs form a complex with MMPs, limiting interaction with the active site. A balance between MMPs and TIMPs is required for wound healing, which is impaired in diabetes patients[114]. Increased protease activity caused by high MMP levels in diabetic wounds causes tissue damage and slows down normal repair processes[115]. This is due to altered MMP expression and decreased TIMP expression in diabetic conditions, which results in high levels of pro-inflammatory and pro-fibrotic cytokines due to increased inflammatory cell activation and invasion, and indirectly affects MMPs through the formation of advanced glycation products which leads to the loss of growth factors, receptors, and matrix proteins essential for wound healing[111,114]. Drugs, therapy that is useful in diabetic wounds are found to act by enhancing collagen synthesis, decreasing inflammatory cytokines, AGEs *etc*. Further, identifying the therapeutic agents that can inhibit MMPs, *i.e.*, MMP-1, MMP-8, and MMP-9 could be important in the management of diabetic wounds.

Autologous stem cells capable of self-renewal and multi-lineage differentiation have been used in diabetic wound. Clinically, bone marrow-derived mononuclear cells and mesenchymal stem cells are the most successful stem cell therapies[116,117]. Besides these, several other targets to promote diabetic wound healing include stimulation of nitric oxide production and up-regulation of endothelial NO synthase and nitric oxide (NO) expression[118-120], a decrease of AGE receptors[121], collagen

generation and epitheliazation *etc*[122-124]. Figure 3 represents plausible drug targets for diabetic wound.

MANAGING DFU: PHARMACOTHERAPY

Hyperglycemic environments worsen the wound situation and delay the wound healing process, thus controlling blood sugar levels is important for the wound healing process. Several antidiabetic medications [*i.e.*, insulin, metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones] found effective in controlling not only blood sugar levels but also promoting the healing of a wound. Metformin was found to be effective in wound healing, which may act by improving epidermis and deposition of collagen, and increasing TGF-β production that may link with angiogenesis process, inflammatory reaction, re-epithelization, and remodeling process. DPP-4 inhibitors may act by increasing the generation of SDF1α, which is crucial for wound repair process[11, 125]. Drugs like simvastatin (enhance VEGF and NO content at wound site) and phenytoin (enhance VEGF and FGF in wound area) have also shown some positive effects in wound healing[11,125].

Infection caused by microbes is a major problem in DFU. Antimicrobial therapy targeting Gram -ve, Gram +ve, anaerobic bacteria, and certain fungi, contributing to the pathophysiology of DFU, is also a key approach. Povidone iodine solution (10%), chlorhexidine, acetic acid (5%), and silver compounds can be used to treat the mild wound. Antibiotics like amoxicillin + clavulanate, ampicillin, dicloxacilline, cephalosporin (*i.e.*, cephalexin, cefoxitin, ceftriaxone, and ceftazidime), quinolones (*i.e.*, ciprofloxacin, levofloxacin), metronidazole, and clindamycin used to cure moderate DFU[126]. Drugs like pipera-cillin/tazobactam + clindamycin, meropenem, imipenem, ertapenem, ampicillin + sulbactam are used to cure severe infections caused by different Gram +ve and Gram -ve bacteria, anaerobes, MRSA, *P. aeruginosa*, while vancomycin, linezolid, and daptomycin can cure MRSA[11]. Cefepime, ceftazidime, meropenem, and piperacillin/tazobactam are recommended to use against *P. aeruginosa;* Metronidazole and clindamycin are used to manage infection caused by anaerobes, while osteomyelitis can be managed with quinolones and linezolid. Further, the effectiveness of different drugs like penicillin, cephalosporin (ceftazidime, ceftriaxone, and cefuroxime), dicloxacillin, vancomycin aztreonam, cefalotin, clindamycin, cefoxitin, gentamicin, imipenem, piperacillin/tazobactam, imipenem, metronidazole, amikacin, levofloxacin, and cefalotin against microbes contributing in DFU infection also established[126]. Dressings with hydrogels, acrylics, hydrofibers, films, hydrocolloids, calcium alginates, polyurethane foam and ciprofloxacin-loaded calcium alginate wafer are also used to control the infection[126,127].

Debridement (elimination of bacterial biofilm and necrotic tissue from wound site), offloading (complete/partial removal of pressure), PRP, EGF, PDGF, FGF, oxygen therapy, negative pressure wound therapy (NPWT), low-level laser therapy (LLLT), extracorporeal shock wave therapy (ESWT), bio-engineered skin substitutes/ soft tissue substitutes (amniotic membrane, autologous stem cell therapy, bi-layered bio-engineered skin substitute, human fibroblast-derived dermis, porcine small intestine submucosa), and maggot therapy are also used successfully to cure DFU[127-129].

In clinical practice, control of blood glucose level, periodical foot screening, patient education, use of therapeutic footware by susceptible people, prophylactic arterial revascularization are important in prevention of DFU[130]. Off-loading in different grades of DFUs (grade 1B, 1C), and diagnosis of diabetic foot osteomyelitis are recommended in grade 1B, 1C, 2C DFU using different screening methods by Society of Vascular Surgery[130]. Surgical debridement to remove necrotic and devitalized tissue, use of proper dressing to create and maintain moist environment, reducing plantar pressure and shear stress (off-loading), vascular assessment in patient with peripheral arterial disease are the vital part of wound care in diabetic people[130,131]. Microbial infection is a major concern in DFU, and in such cases, use of antimicrobial agents is advised conserving extent of infection[131]. A number of adjuvant therapy as discussed in previous section are also used for effective wound healing. Further, adequate glycemic control is important also in acceleratd healing of DFU's[130,131].

RECENT APPROACHES IN CLINICAL TRIALS

Several treatments /medicines have been successfully investigated clinically for their beneficial effects on the diabetic wound, especially in DFUs which was tabulated in Table 1[132-159].

PRP is an important treatment approach investigated in DFU. A systematic review with meta-analyses of 10 studies reported that PRP promotes chronic diabetic wound healing (RR = 1.32; 95%CI: 1.11-1.57, I^2 = 15%) by reducing the volume and time of wound healing[160]. PRP may act *via* promoting the proliferation of wound cells, upregulation of cyclin A and cyclin-dependent kinase 4 proteins, modification of macrophage phenotype, reduction of TNF-α, enhancement of TGF-β and VEGF, increased secretion of fibroblast of collagen type I and III[161].

Table 1 Clinical trial of few therapeutic agents/approaches in the management of diabetic wound

Ref.	Type	Drug/ product /approach investigated	Type and number of participants	Type of wound	Observation
[132]	Homeopathic medicine	Silicea, Sulphur, Lycopodium, Arsenic album, Phosphorus	Observational study, 156 patients	DFU	Ulcer assessment score reduced significantly ($P < 0.05$) after treatment. Silicea, sulphur ($n = 11$), lycopodium, arsenic album, phosphorus were found more effective. Although, the effect of homeopathic therapy alone is difficult to establish
[133]		Silicea	Observational study, 22 patients	DFU	Positive and encouraging result of silicea in ulcer healing was reported. DFU assessment score was measured, and mean symptom scores at the end of the treatment were found to reduce significantly ($P < 0.05$)
[134]	Herbal Products	ON101 cream (contain extract of *Plectranthus amboinicus* and *Centella asiatica*)	Phase 3 RCT, 236 participants	DFU	Incidence of complete healing in ON101 and comparator group was 60.7% and 35.1% respectively. Although, the number of adverse events in the ON101 group was 7 *vs* 5 in the comparator group. ON101 produced a better healing effect compared to absorbent dressing alone
[135]		Intravenous Semelil (a naive herbal extract)	RCT, 25 participants	DFU	Mean foot ulcer surface area reduced significantly in semelil (i.v. route) group and the average wound closure in semelil group was significantly more than control group (64% *vs* 25%, $P = 0.015$). Semelil in combination with conventional therapy showed better effect than conventional therapy
[136]		Olive oil	Double blind RCT, 34 participants	DFU	Degree of ulcer, color, surrounding tissues, the status of ulcer and ulcer drainages were evaluated after topical application of olive oil. Complete ulcer healing in the treatment group was significantly better than the control group (73.3% *vs* 13.3%, $P = 0.003$). Olive oil treatment significantly reduced ulcer area and ulcer depth. Olive oil in combination with routine care was better than routine care alone
[137]		Polyherbal formulation (contain *G. glabra, M. paradisiaca, C. longa, P. odaratissimus, A.e vera, C. nucifera* oil)	Open label, phase III, comparative study, 40 participants	DFU	Polyherbal formulation was found effective similar to that of standard silver sulphadiazine cream
[138]		Semelil (ANGIPARS™, contain *Melilotus officinalis*)	Clinical study, 10 participants	DFU	ANGIPARS™ was found effective in reduction of wound size by at least 50% during 8 wk period
[139]	PRP	PRP gel	Single-arm clinical trial, 100 participants	DFU	PRP therapy (2 mL/cm^2 of ulcers) was found highly effective in the treatment and healing of non-healing chronic DFUs
[140]		PRP	Prospective RCT, 20 participants	DFU	Wound healing time was estimated as 8 wk which is superior to the control group. People treated with PRP it found more effective in wound healing
[141]	Human EGF (hEGF)	Recombinant hEGF	Prospective, open-label trial, crossover study, 89 participants	DFU	Wound healing was noted within an average of 46 d in patients who were treated with 0.005% EGF twice a day. Topical application of hEGF combined with hydrocolloid dressing showed promoting healing effect in chronic DFU
[142]		Regen-D 150 (hEGF gel-based product)	RCT, 50 participants	DFU	Complete ulcer healing was detected in 78% population against 52% population in the placebo group. Collagen and fibroblasts were significantly developed in the treated group. The application of hEGF can be helpful to promote wound healing and in preventing leg amputations
[143]	PDGF	rhPDGF	RCT, 50 participants	DFU	Wounds contracted more in rhPDGF-treated group compared to the control group (38.55% *vs* 12.79%; $P \leq 0.001$). Dressing with rhPDGF was found more effective and promoted safe wound healing
[144]		PDGF gel	RCT, 29 participants	Diabetic lower extremity ulcer	100% of ulcers were healed in subjects who received PDGF compared to 76.4% of wound healing in placebo group. The study confirms the effectiveness of PDGF gel
[145]	FGF	bFGF	Double-blind RCT, 150 participants	Non-ischaemic diabetic ulcer	Wound cure rate in 0.001% bFGF, 0.01% bFGF and control group was 57.4%, 66.7% and 46.8%. The area of the ulcer was also significantly decreased in bFGF treated groups. bFGF accelerates wound healing in diabetic people
[146]	Oxygen therapy	Topical oxygen therapy	RCT, 145 participants	DFU	A significant decrease in wound area was reported in the topical oxygen therapy + standard care group (70%) compare

				to the standard care group (40%) Addition of topical oxygen therapy with standard care facilitates wound closure in a better way
[147]		Hyperbaric oxygen therapy	RCT, 75 participants	Chronic DFU	Complete healing of ulcer index was reported in 52% of participants who received hyperbaric oxygen therapy after 1 year, which was 29% in the placebo. Adjunctive treatment with hyperbaric oxygen therapy may facilitate the healing of foot ulcers
[148]	NPWT	NPWT	Prospective randomized study, 55 participants	DFU	Granulation tissue formation (91.14% *vs* 52.61%, *P* < 0.001) and a decrease in the size of ulcer size (40.78% *vs* 21.18%, *P* = 0.008) were reported in the NPWT group after 14 d. Duration of hospital and time for complete coverage of the wound with granulation tissue was significantly less in the NPWT group. NPWT led to an early decrease in the size of the ulcer, formation of more granulation tissue, and wound healing
[149]		NPWT	RCT, 55 participants	DFU	The rate of ulcer healing was found higher in the NPWT group (*P*-value 0.01). NPWT leads to a higher rate of healing, and causes a significant decrease in ulcer surface area, size, and depth of the wound, reducing the risk of amputations
[150]	Phototherapy	LLLT	RCT, 23 participants	DFU	Ulcers size reduced significantly in 4th week in LLLT group (*P* = 0.04). More patients healed completely in LLLT group compared to the placebo group. Meantime of complete healing in patients treated with LLLT was 11 wk *vs* 14 wk in placebo patients. LLLT promotes the healing process of chronic DFU, and reduces the time required for wound healing
[151]		LLLT	RCT, 56 participants	DFU	Increment in total hemoglobin was more using the highest intensity configuration compare to the lower intensity setup in patients with DFU. A decrease in the very-low frequency/low frequency ratio, slightly more than the highest intensity in DFU people was observed. LLLT was found to increase blood flow and regulation of the autonomic nervous system in patients with DFU
[152]	ESWT	ESWT	Single-blinded RCT, 38 participants	DFU	Patients received shock wave therapy 2/week for a total of 8 treatments. Average healing time was lower in ESWT-group when compared with the control group (64.5 *vs* 81.17 d, *P* < 0.05). AT 20 wk, 54% of ulcer healed completely in ESWT-groups compared to 28.5% in the control group
[153]		ESWT	Prospective RCT, 23 participants	DFU	At 7 wk, the mean reduction in ulcer area was 34.5% (CI, 0.7-68.3) in the ESWT group and 5.6% (CI, -42.1-53.3) in the control group. ESWT also enhances tissue oxygenation
[154]	Stem cell therapy	Topical application of MSC	Clinical case study of three patients	Neuropathic DFU	MSCs at low doses enhance the re-epithelialization of DFU. MSCs may start early to reduce overall wound closure time
[155]		HUCMSCs	RCT, 56 participants	DFU	Patients in HUCMSCs (endovascular infusion and injection around the foot ulcer) experienced greater and betterment in skin temperature, transcutaneous oxygen tension, ankle-brachial pressure index, and claudication distance. Three months after treatment significant enhancement in neovessels, and complete or gradual ulcer healing was observed in the experimental group
[156]	NO generating approach	EDX110 (nitric oxide generating medical device)	RCT, 135 participants	DFU	At 12 wk, EDX110 use resulted in 88.6% reduction in median wound area compared to 46.9% for the control group (*P* = 0.016). EDX110 was found to improve foot wound healing in diabetic people significantly by reducing the ulcer area
[157]	Other Approaches	Bemiparin (low MW heparin)	RCT, 70 participants	DFU	In bemiparin group, the ulcer improvement rate was 70.3% compared to 45.5% in the placebo group. Though, complete healing rates found similar in both groups at 3 mo were, as were the number of adverse events. Bemiparin is better than a placebo in the management of DFU and has few side effects
[158]		Honey dressing	RCT, 348 participants	DFU	In 75.97% of cases wound healed completely after honey dressing in comparision to 57.39% of case in the saline dressing group. The homey dressing also reduced the median wound healing time (18.00 d) compare to the control group (29.00 d). Honey is an effective dressing substance compared to conventional dressings
[159]		Omega-3–rich fish skin grafts	RCT, 49 participants	DFU	At 12 wk, 67% of foot wounds were completely closed compared with 32% in the standard care group. Study findings indicated that fish skin graft is useful in the treatment of chronic DFUs that do not heal with standard treatment

DFU: diabetic foot ulcers; RCT: randomized controlled trials; PRP: platelet-rich plasma; hEGF: Human endothelial growth factor; rhPDGF: Recombinant human platelet-derived growth factor; PDGF: platelet-derived growth factor; bFGF: Basic fibroblast growth factor; NPWT: Negative pressure wound therapy; LLLT: Low-level laser therapy; ESWT: Extracorporeal shock wave therapy; MSC: Mesenchymal stromal cell; HUCMSCs: Human umbilical cord mesenchymal stem cells; NO: nitric oxide.
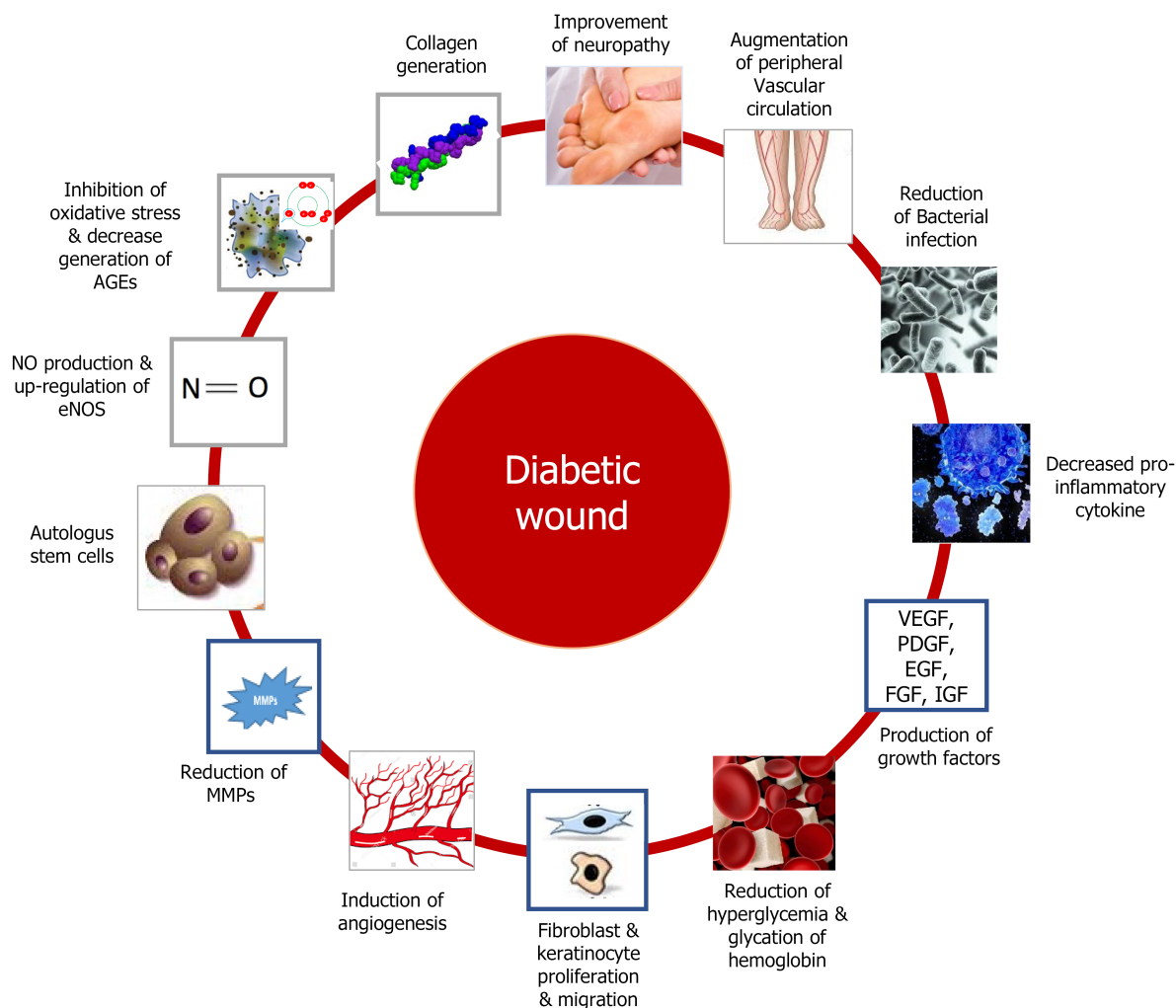
DOI: 10.4239/wjd.v13.i9.696 **Copyright** ©The Author(s) 2022.

Figure 3 Plausible drug targets for diabetic wound. AGEs: Advanced glycation end-products; VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; IGF: Insulin-like growth factor.

A systematic review of 26 randomized controlled trials (RCTs) examined the usefulness of different recombinant proteins and growth factors in the treatment of DFU. EGF can be used as intralesional injection, topical cream, or gel. This meta-analysis reported that EGF significantly improves wound healing and the study failed to find a significant effect of EGF in reducing the risk of amputation[162]. Decreasing the level of circulating C-reactive protein, decreasing NFκB1, TNF-α, and IL-1a expression, and increasing the wound expression of platelet-derived growth factors (PDGF)-B, cyclin-dependent kinase 4, P21, TP53, angiopoietin 1, collagen 1A1, MMP-2, and TIMP-2 after the treatment with hEGF may be linked to its beneficial effect[161]. Recombinant human PDGF (rhPDGF) also exhibits their beneficial effect in several clinical studies[143,144], but few clinical studies also failed to find statistically significant effects of rhPDGF compared to the control group[163,164] when used to cure DFU. The effectiveness of PDGF may be related to the promotion of fibroblast and leukocyte migration, and synthesis of extracellular matrix[161]. FGF, a family of cell signaling proteins, is found to stimulate angiogenesis, induce fibroblasts proliferation, and promote wound healing. About 23 subtypes of FGF from 7 subfamilies were identified[165]. Some clinical studies have reported the beneficial effect of FGF in diabetic wound[145], some studies failed to report the advantageous effect of FGF over the placebo group[166], while clinical studies reported the beneficial effect of combined use of human EGF and acidic FGF on wound healing in the later stage[167]. Very few clinical studies evaluated the effectiveness of granulocyte-colony-stimulating factor, topical telbermin, epoetin-β, talactoferrin, TGF-β2 in

the diabetic wound. But the results are inconsistent[162].

Oxygen therapy is found to improve cell metabolism and energy, decrease proinflammatory cytokines and ROS, and promote the synthesis of matrix and wound repair[161]. Few clinical studies confirmed the beneficial effect of hyperbaric as well as topic oxygen therapy in promoting diabetic wound[146,147]. A systematic review and meta-analysis of 20 RCTs and 1263 trials analysed that hyperbaric oxygen therapy confer benefits in DFU treatment by increasing the healing of ulcers (relative risk, 1.901; 95%CI: 1.484-2.435, *P* < 0.0001), reducing healing time, and also decrease the risk of major amputation[148].

It was evaluated that NPWT results in macro- and micro-deformation that stimulate different wound healing cascade like promotion of tissue granulation, epithelialization, proliferation of vessel, neo-angiogenesis, pro-angiogenic condition, removal of surplus extracellular fluid, anti-inflammatory effect, increase expression of VEGF, FGF2, modification of circulating micro-RNAs, alteration of DNA methylation of genes linked with wound repair[161,168]. Liu *et al*[169] in their study (meta-analysis of 11 RCTs) concluded that NPWT is a safe, cost-effective and effective strategy in the treatment of DFU, while Liu also evaluated 11 RCTs and found that compared with wound dressings NPWT may enhance the proportion of wounds healed, decrease the time of postoperative foot wound healing[170].

LLLT was found to increase blood flow and regulation of the autonomic nervous system in patients suffering from DFU[151]. Reduce wound inflammation, enhance fibroblasts and angiogenesis[161], which may play an important role in diabetic wound healing. A metanalysis of 13 RCTs that included 413 patients concluded that LLLT significantly enhanced complete healing rate (RR = 2.10, 95%CI: 1.56-2.83, *P* < 0.00001), decreased wound ulcer area, and reduce mean healing time of wound healing in patients suffering from DFU[171].

Huang *et al*[172] performed a meta-analysis of 8 RCTs and concluded that ESWT treatment reduced wound surface area in greater proportion, enhances re-epithelialization and can reduce treatment inefficiency. ESWT is useful as an adjuvant strategy in the management of DFUs, which can improve the complete wound cure rate and reduce the healing period of DFUs. ESWT may enhance the angiogenesis process, decrease macrophage number, and enhance the production of macrophage of growth factors from macrophages that help in the healing of wound[161].

In light of current evidence, it can be suggested that stem cell-based therapy (delivery through both local and systemic route is effective to heal DFU and considered a promising regenerative medicine, and mechanisms of stem cell therapy include improved angiogenesis, decrease inflammation, ameliorating neuroischemia, improved collagen deposition, *etc*.[173].

Wound healing in diabetic people can be promoted by providing endogenous or exogenous NO. Products (*i.e.*, patches/ matrices) that release NO are used to treat diabetic wounds by different mechanisms like enhancement of angiogenic activity, endothelial cell proliferation, conferring antimicrobial substances, and promoting cell migration to the injured site[174]. Only a few clinical studies have reported the beneficial effects of NO-releasing devices, and several products are in the clinical trial.

Homeopathic medicines (like silicea, sulphur, lycopodium, and arsenic) were also investigated in the clinical trial and concluded that homeopathic medicine may be useful in the management of diabetic wounds[132,133]. Several other products, like honey, fish skin grafts, *etc.,* were also clinically investigated for their beneficial effects against DFU[158,159]. Further, several herbal products were also successfully investigated in the treatment of diabetic wound[134,135,136-138].

MEDICINAL PLANTS AND PHYTOCONSTITUENTS IN DIABETIC WOUND

Medicinal plants and phytoconstituents always represent an important, effective and alternative treatment strategy to cure diseases. Phytochemicals have showed their effectiveness in different diabetes complications. Anti-inflammatory mechanism of phytochemicals is considered important in the management of diabetes wound. Epigallocatechin gallate in pre-clinical investigation was found to reduce reduced levels of IL-1β, TNF-α and IL-6, producing inhibition of Notch signaling and accumulation of macrophage at a wound site. Kaempferol, is an important dietary flavonoid found to exert different pharmacological activities, including antioxidant, anti-inflammatory and cardioprotective activity. An ointment containing Kaempferol was found effective in diabetic excisional and non-diabetic incisional wounds in experimental animals[175]. Flavonoids an important class of phytoconstituents, exerted anti-inflammatory and antioxidant effect, and also enhances angiogenesis and re-epithelialization. Preclinical trials found the effectiveness of isoliquiritin, isoflavonoid, naringenin, dihydromyricetin, dihydroquercetin, quercetin, hesperidin, kaempferol, proanthocyanidins, icariin, puerarin, rutin, genistein, luteolin, rutoside, silymarin, daidzein, genistein, and epigallocatechin gallate to cure wound[174]. Flavonoids positively regulate MMP-2, MMP-8, MMP-9, MMP-13, Ras/Raf/MEK/ERK, PI3K/Akt, and NO pathways. Phytochemicals are found to reduce oxidative stress, expression/release of proinflammatory/inflammatory cytokines, *i.e.*, TNF-α, IL-1β, IL-6, NF-κB and upregulate IL-10 and antioxidant enzymes. Flavonoids also act on macrophages, fibroblasts and endothelial cells by facilitating expression/release of TGF-β1, VEGF, angiopoietin, tyrosine kinase with immunoglobulin and epidermal growth factor homology domains, and small mothers against

decapentaplegic 2 and 3[176]. Oguntibeju[177] in his paper highlighted different medicinal plants like *Rosmarinus officinalis*, *Carica papaya*, *Radix rehmanniae*, *Annona squamosa*, *Catharanthus roseus*, *Centella asiatica*, *Acalypha langiana*, *Hylocereus undatus*, *Punica granatum*, *Aloe vera*, and *Martynia annua* that has been investigated in the treatment of diabetic wound. Benefits of the plants may link to different mechanisms like an increase in fibroblast cell, fibroplasia, increase in collagen formation, enhancement of tissue regeneration, angiogenesis, antimicrobial, anti-inflammatory and antioxidant effect. A recent clinical study established the effectiveness and safety of nano-hydrogel embedded with quercetin and oleic acid when used in the management of lower limb skin wound in diabetic patients. The formulation effectively treated the wound and reduce the wound healing time compared to the control group[178]. Infections caused by different microbes like *Staphylococcus aureus*, *Streptococcus* β-hemolytic, *Pseudomonas aeruginosa*, *Peptostreptococcus spp.*, *Proteus spp.*, *Prevotella spp.*, *Bacteroides spp.*, *Clostridium spp*. and anaerobes are posing a serious situation in diabetic people[126]. Medicinal plants and phytochemicals with antimicrobial activity may also play an important role in the management of diabetic wound. Several plants have shown their potential against the microbial strain responsible for infection in the diabetic wound[126]. Formulation designed with *Momordica charantia*, *Actinidia deliciosa*, *Aloe vera*, *citrus fruits*, *Sida cordifolia*, *Nigella sativa*, *Curcuma longa*, and *Azadirachta indica* has shown their potential in the treatment of diabetic wound[126]. Isoflavones isolated from plant sources were also found to be effective against DFU bacteria[179] Phytofabricated silver nanoparticles (*Aerva lanata* reduced silver nanoparticles) at 20 μg/mL were found highly effective against multi antibiotic-resistant DFU isolates like *E. coli*, *P. aeruginosa*, *S. aureus, S. subtilis*. Identified phytochemicals of *A. lanata* include rutin, quercetin, kaempferol, gallic acid and ellagic acid[180]. The use of phytoextracts/active compounds may be considered as an important strategy for addressing the wound problem associated with DM in a better way.

CONCLUSION

Diabetes adversely acts on the phases of normal wound healing phases, i.e., hemostasis, inflammatory phase, proliferative phase, re-epithelialization and remodeling phase, and poses a big burden on the quality of life of a diabetic individual. Hyperglycemia can trigger oxidative stress, increase inflammatory cytokines, interrupt angiogenesis, decrease the functioning of fibroblast and keratinocyte, induce neuropathy associated events, increase MMPs, and reduce TIMPs that is responsible for impaired states of wound healing. An understanding sequence of the molecular and cellular cascade, epigenetic mechanisms, microbial perspective, complexity and plasticity of impaired wound healing in diabetic conditions is required for targeted research focusing on treatment of diabetic wound. Pharmacotherapy/strategy involving angiogenesis stimulation, growth factors, cytokines modulators, MMP inhibitors, ECM stimulators, anti-inflammatory drugs, antidiabetic agents, antimicrobial drugs, debridement, offloading, PRP, oxygen therapy, NPWT, LLLT, ESWT, stem cells, bio-engineered substitutes, and various natural-based products have shown their benefit. There has been a lack of quality-based evidence of efficacy of different adjuvant therapies tested through different clinical trials, thus more structured and quality studies are required. Indeed, the utilisation of medicinal plants/products in diabetic wound care holds prodigious potential in the future, and the development of innovative pharmaceutical formulations for advanced wound care is equally critical. Effective diabetic wound management necessitates a combination of techniques, including medication and non-pharmacological intervention. Hence, the treatment strategy of the future can only succeed if research concentrated on plausible drug targets after comprehending the inherent pathological complexities, evaluating non-pharmacological approaches through well-designed clinical trials, and targeting natural sources for new drug development.

FOOTNOTES

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