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Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing

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ABSTRACT

Wound management in diabetic patient is of an extreme clinical and social concern. The delayed and impaired healing makes it more critical for research focus. The research on impaired healing process is proceeding hastily evident by new therapeutic approaches other than conventional such as single growth factor, dual growth factor, skin substitutes, cytokine stimulators, cytokine inhibitors, matrix metalloproteinase inhibitors, gene and stem cell therapy, extracellular matrix and angiogenesis stimulators. Although numerous studies are available that support delayed wound healing in diabetes but detailed mechanistic insight including factors involved and their role still needs to be revealed. This review mainly focuses on the molecular cascades of cytokines (with growth factors) and erstwhile factors responsible for delayed wound healing, molecular targets and recent advancements in complete healing and its cure. Present article briefed recent pioneering information on possible molecular targets and treatment strategies including clinical trials to clinicians and researchers working in similar area.

1. Introduction

Diabetes is a multifaceted metabolic disease that affects more than 340 million individuals and about 20% of them develop diabetic wounds worldwide [1]. Leg or foot ulcers are most common wounds in diabetic patients. Diabetic patients have declined ability to metabolize glucose resulting in hyperglycaemic conditions which further complicate the wound healing process. This can result in stalled chronic wounds. The incidence of delayed healing process in diabetic patient is increasing globally due to lack of preventive and control measures. About 2.5%–15% of yearly world-wide health budgets are consumed on diabetes mellitus and diabetic wounds stake a major part. WHO report speculate that diabetes will be the 7th foremost reason for death in 2030. In 2014, 9% of adults had diabetes and was the reason for death of 1.5 million patients in 2012. More than 80% of diabetes deaths occur in low- and middle-income countries [1,2]. Approximately 50%–70% of all the limb amputations are because of diabetic wounds and it was reported that in every 30 s, one leg is amputated due to diabetic wounds in worldwide [3].

Wound healing is a multifaceted and dynamic process which results in the restoration of anatomic integrity with analogous function. Prime requirement for wound management is rapid and complete healing without spreading infection and sepsis. Acute wounds generally heal with ease without any issue. The major concern involves age related alteration in normal physiological functions like deprived blood circulation, obesity, diseases like diabetes and stressed environmental conditions. Based on their healing potential wounds are indicated into two forms i.e. chronic and acute one. Chronic wounds include tissue injuries which do not heal in an organized set of stages and takes more than 12 weeks for healing [4,5]. Normally, healing process starts with haemostasis that checks the blood loss and invasion of microbes to wounded area. This phase is rapidly followed and overlapped by an inflammatory phase, in which pro-inflammatory cells neutrophils up-regulate (initially) followed by macrophages which clean up debris and pathogens along with growth factors and other cytokines and cells. Proliferative phase overlaps inflammatory phase in which new tissue, new blood vessels (angiogenesis) and matrix construction is initiated to fill the wounded area. The final remodelling phase then increases the tensile strength of the extracellular matrix and reduces the blood supply to the damaged area [6–9].

DWs[1] are one of the major concerns which mainly includes leg ulcer/diabetic ulcer. Diabetes delay healing process because it impairs each phase of wound healing i.e. haemostasis, inflammation, proliferation and remodelling phase, which has a long-term negative effect on quality of life, morbidity and mortality (Fig. 1). DWs are characterized by delayed acute wounds and chronic wounds unveiling impaired healing due to a postponed, incomplete, or uncoordinated

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[1] Diabetic Wounds

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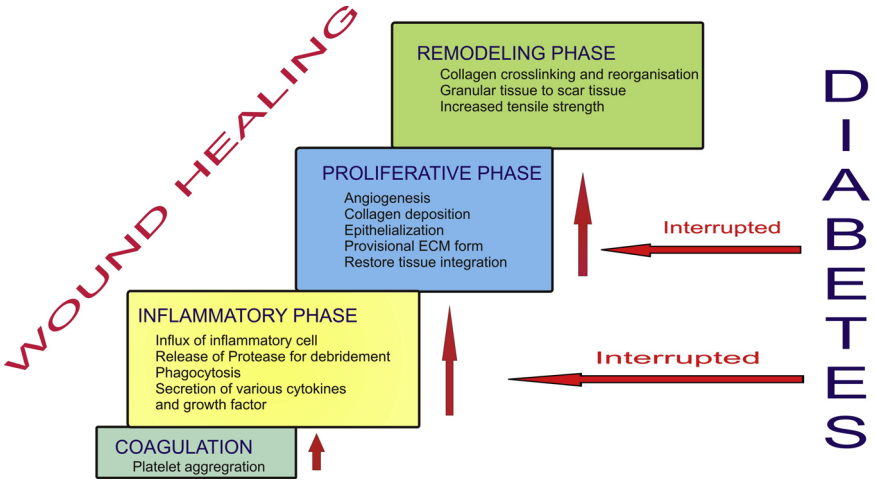

Fig. 1. Interruption of normal wound healing process in diabetes.

healing process. DWs exhibit a persistent inflammatory phase associated with an impediment in the formation of mature granulation tissue and reduction in wound tensile strength. This may be due to the vascular damage resulting in ischemia [10,11]. Each wound is an alarm for health and needs instant care. Generally, wounds are of two types on the basis of origin- external and internal. External origin wounds are like cuts, injuries, burns and bruises. These external wounds may frequently go unnoticed by diabetic patient because of peripheral neuropathy. Internal origin wounds like skin ulcers and calluses cause destruction of skin and nearby tissues with chances of bacterial infection.

Existing standard approach employs series of medical treatments to clean and eradicate the infected tissue, and maintain moisture with adequate blood supply [12]. Recent studies have engaged in understanding the critical factors that influence healing process. Although a great deal remains to be learned, these studies may lead to therapeutics that will promote proper tissue repair and improve impaired wound healing. Present review is an attempt to reveal the molecular events responsible for delayed wound healing, molecular targets for complete healing and recent advancements in its management.

2. Mechanistic insight

Diabetes delays the healing process leading to a non-healing wound including various complications with associated psychiatric stress and depression. These complications consist of functional limitations, difficulty in walking, and infection like cellulitis, abscess, osteomyelitis, gangrene, and septicaemia. Impairment of healing in diabetic patients is familiar but the link between patho-physiology and impaired wound healing in diabetes is still an unknown etiology. The healing process necessitates collaboration between inflammatory cells and biochemical mediators stimulated by various factors. However, alteration of the cellular and biochemical factors and activities have been implicated in the failure of wound healing in diabetics.

Cells involved in wound healing process are neutrophils, monocyte, macrophages, keratinocytes, fibroblasts, T cells, B cells, mast cell and endothelial cells. These cells are actively involved in the production and regulation of various cytokines and growth factors. Monocyte, which later transform into macrophages is the foremost producer of pro-inflammatory cytokines IL-1β[2], TNF-α[3], IL-6[4] and VEGF[5], IGF-1[6] and TGF-β[7] in both diabetic and non-diabetic conditions. Neutrophils along with T and B cells are also a significant producer of TNF-α, IL-10 and other cells, keratinocytes, fibroblasts, mast cells and endothelial cells. These cells also contribute in production of VEGF, IGF-1 and TGF-β [113]. Macrophages are pivotal contributor in healing. Hyperglycaemia and oxidative stress changes the epigenic code that results into change in macrophage polarization and its modulation. Dys-regulated macrophage polarization is one of the main reasons in delayed wound healing [13,14]. Studies revealed that in diabetes, a complex mechanism involve at molecular level which is responsible for delayed wound healing. Activities like sustained production of pro-inflammatory cytokines, impaired angiogenic response and microvascular complications [10], impaired macrophage and neutrophils function [15], impaired keratinocytes and fibroblast migration and proliferation and impaired production of healing-associated factors like impaired growth factor production has been reported in diabetic animal models [16].

The phases of healing process in diabetic patients are also stalled by other factors, including specific metabolic deficiencies, impaired physiological responses like hypoxia due to glycation of haemoglobin and alteration of red blood cells membrane and narrowing of blood vessels [17]. Hypoxia involves decreased oxygen supply to wounds due to narrowed blood vessels. Glycation of haemoglobin causes deficient supply of nutrients and oxygen to tissue which further delay the healing process. Hypoxia/glucose deficiency and deformed proteins produce a stress response to cell by accretion of unfolded proteins within endoplasmic reticulum known as UPR[8] . This UPR is activated just after tissue or skin injury and linked to production of pro-inflammatory mediators. DWs showed sustained induction of UPR along with augmented expression of the pro-inflammatory chemokine as compared to normal wounds [18].

Local ischemia due to microvascular complications in diabetes considerably delays wound healing. miRNAs[9] are a class of noncoding RNAs of 19–24 nucleotides in length that link in numerous physiological processes and play an important role in these complications. Altered levels of miRNAs have been reported in various diseases and impaired wound healing [19]. One of the miRNAs, MiR-210 is induced in hypoxic situations and targets E2f3 that reduce keratinocyte proliferation in wound healing [20]. MiR-200b decreases angiogenesis by steering globin transcription factor 2 and VEGFR2[10] [21]. Similarly various miRNAs like miR-130a, miR-21, miR-146a, miR-198 and miR-

[2] Interleukin-1β
[3] Tumour necrosis factor-α
[4] Interleukin-6
[5] Vascular endothelial growth factor
[6] Insulin-like growth factor-1
[7] Transforming growth factor-β
[8] unfolded protein response
[9] Micro RNA
[10] Vascular endothelial growth factor receptor

26a involve in diabetic wounds that affect epithelization, delay inflammation, fibroblast migration, keratinocyte migration, re-epithelialization and angiogenesis [22,23]

Along with these, there are some physiologic factors like increased serum matrix metalloproteinase-9 [24], impaired collagen accumulation and variation in the ratio of collagen types, dysregulation in the neuropeptide expression in the skin along with a suppressed inflammatory response [25], deficiency of thrombin-activatable fibrinolysis inhibitor [26], AGE[11] modification of PDGF [27], decreased number of epidermal nerves, epidermal barrier function [10] and misbalance between the accumulation of ECM components and their remodelling by matrix metalloproteinase [17,28] are responsible for slow healing process in diabetic patients (Fig. 2).

2.1. Roles of chemokines, free radicals and oxidative stress

In last decades, noteworthy evidences have been generated to support a number of mechanisms as shown in Fig. 3 which influence diabetic wounds including polyol pathway, hexosamine pathway, diacylglycerol pathway, nitric oxide blocking, PKC (protein kinase C) pathways, formation of AGEs i.e. maillard reaction and intraglomerular hypertension induced by glomerular hyperfiltration which lead to neuropathy. These mechanisms are stimulated by mitochondrial overproduction of reactive oxygen species [29] and oxidative stress. In diabetes, high oxidative stress plays a major role in complications and impaired healing process. One of the transcription factor NRF2[12] controls the adaptive response to oxidative stresses as well as decreased apoptosis, promote cell migration, proliferation, and cell differentiation [30]. High glucose and oxidative stress activates NRF2 to control and repair the impairment. Long et al had shown that inducing NRF2 activation reduced diabetes-induced oxidative stress levels, regulates the expression MMP-9, TGF-β, migration and proliferation-related genes via direct or indirect mechanisms [31].

ATF-3[13] is a stress-inducible gene, and its expression is induced B-cell dysregulation and diabetic complications [32]. The irregular pro-inflammatory response activates ATF-3 and iNOS and induces oxidative stress, which might be responsible for the prolonged healing processes. Badr et al revealed that irrationally up-regulated expression of ATF-3 and iNOS tailed by an increase in free radical levels and rise in caspase-3,-8, and -9 activityare responsible for impaired cellular differentiation and remodelling phase in healing process [33].

Numerous proinflammatory cytokines plays a major role in leukocyte accumulation (monocytes /macrophages/ neutrophils/ immature dendritic cells) like MIP1α[14], MIP-2[15] and KC[16] and human β-defensin (HβD 1, 2, 3) as antibacterial in healing process. CX3CL1[17] is stated as a soluble chemokine and membrane-bound form on the surface of cells promoting macrophage and fibroblast accumulation [34–36]. Badr et al. revealed that abnormal expression of MIP1 α, MIP-2, CX3CL1, reduce level of HβD 1, 2 and 3, irregular activation of STAT3[18] and decline in the activation of AKT/PKB (serine/threonine protein kinase B) and NF-κB[19] . All these collectively contribute tointerrupt healing in diabetic wounds [34,37].

Diabetic peripheral neuropathy lead to sensory, motor and autonomic dysfunction, each of which contributes to delayed wound healing. In sensory neuropathy, sensation to pain either is lost or absent creating most important threat for the growth of diabetic wounds. Abnormal glycation of nerve cell proteins and the unfortunate activation of protein kinase C due to hyperglycaemia and oxidative stress lead to nerve dysfunction and ischemia [38]. Lack of protective sensation in diabetic wounds leads to unnoticed progression of wounds to worse. Recently Huang et al., reported that alteration in the Akt/mTOR pathway results in impaired wound healing in diabetes induced rat model [39]. Similarly, Lima et al reported, Insulin induces activation of insulin signalling pathways i.e IR/SHC/ERK and IR/IRS/PI3K/AKT pathways in wound healing. By inducing these pathways it increases VEGF and SDF1a tissue expression, increased eNOS phosphorylation, angiogenesis and improved healing in diabetes [40]. Studies revealed the role of matricellular proteins in wound healing which linked with the proteins of the ECM and connecting them to cell surface receptors. One of the matricellular proteins, AL-4[20] facilitates keratinocyte migration, reepithelialization and angiogenesis. AL-4 can connect with integrin β1, and activate the SRC, ERK, and AKT signaling cascades and start JAK1/STAT3 activation. Activated STAT3 can induce the up-regulation of iNOS[21] expression and increase NO production from the keratinocytes in the wound tissue and promote angiogenesis. Normally AL-4 expression has been low in normal skin and is significantly elevated upon injury. But in case of diabetic patient, AL-4 expression remains low, that delayed the healing process by affecting angiogenesis and re-epithelialization [41].

2.2. Role of immune system

Suitable co-ordination of innate immune system has an important role in wound healing. TLRs[22] are important source for the initiation of the innate immune and inflammation response. Down regulation of TLRs-2 in injured tissue impairs or weakens the immune system and inflammation response [42–44] in diabetic patient which causes reduced chemotactic effect that delays the recruitment of various inflammatory cells. Diabetic patients are highly susceptible to infection caused by delayed wound healing and immuno-suppression [42]. Bacterial connections on the wound are important in the etiology of diabetic wounds and it forms biofilms. These biofilms provide a safeguard to microbes from antimicrobial agents and immune system and interrupt the healing process. It is the most common reason of lower limb amputation in diabetic wounds [45].

Inflammatory cells like neutrophils, monocyte, T cells, B cells and mast cell play a chief role in the immunity. Dysegulation of these cells may be decisive in the inhibition of diabetic host immunity. Elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α in diabetes causes interrupted inflammatory cascade, hyperinflammation and insulin resistance. Elevated level of TNF-α may be due to accumulation of effector T cells. Maura et al found lower naive T-cell number and a poorer T cell receptor (TCR-Vβ) range in diabetic wound patients that lead to the accumulation of effector T cells [46].

Immunity is also influenced by high level of AGEs inducing production of various cytokines such as IL-6 and TNF-α. AGEs also obstruct the collagen production, induces apoptosis, excessive immune-responses and negative regulations of the cell physiology leading to impaired healing [47]. Mast cells are potent releaser of angiogenic factors like FGF, VEGF, and TGF-β1 [48]. Various studies support the role of mast cells in wound healing as they act together with macrophages, endothelial cells, and fibroblasts. It plays an important role in matrix restructuring and disturbs the balance between pro-angiogenic factors and anti-angiogenic factors in wound tissues [49]. Bevan et al revealed that in genetically diabetic mice, there was delayed vascular regression due to decrease in the number of mast cells and their dysfunction [50]. Nishikori et al demonstrated the role of mast cell in diabetic wound.

[11] Advanced glycation end-products
[12] Nuclear factor-E2-related factor 2
[13] Activating transcription factor-3
[14] Macrophage inflammatory proteins 1α
[15] Macrophage inflammatory proteins 2
[16] Keratinocyte derived chemokines
[17] Fractalkine
[18] Signal transducer and activator of transcription 3
[19] nuclear factor-κB
[20] Angiopoietin-like 4
[21] Inducible nitric oxide synthase
[22] Toll like receptors

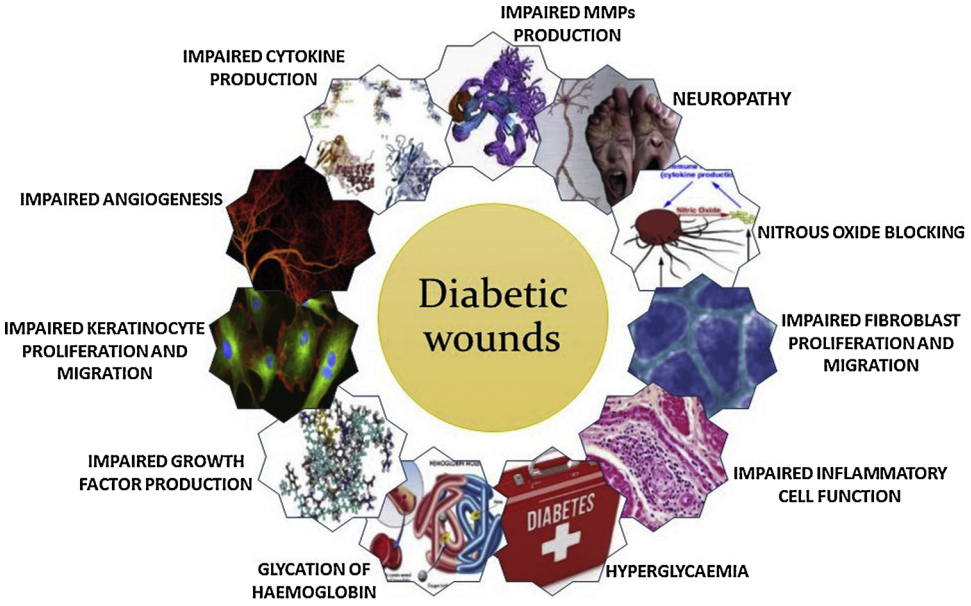

Fig. 2. Factors responsible for Diabetic Wounds.

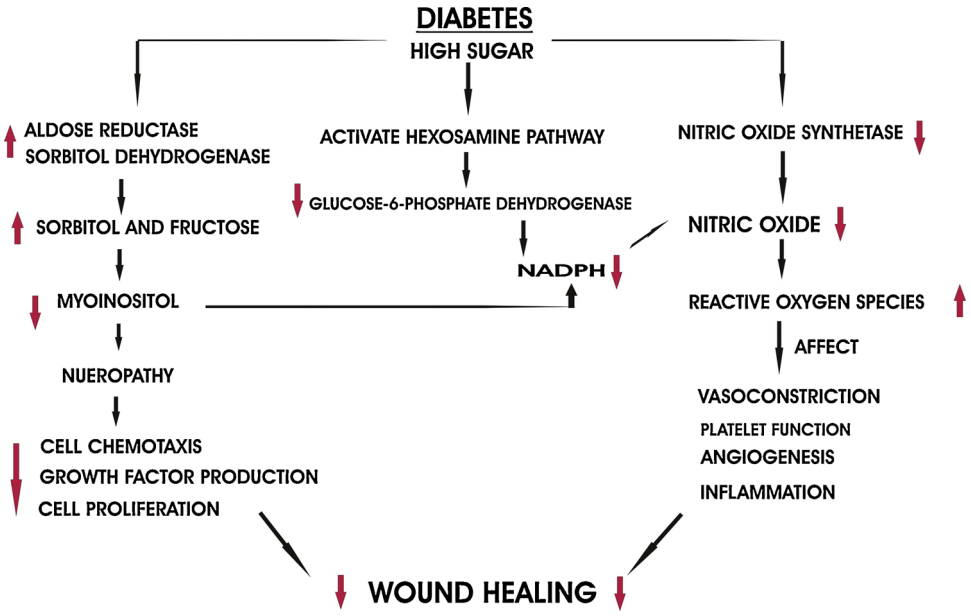

Fig. 3. Major pathways responsible for decreased wound healing in diabetes [4].

They concluded impaired proliferative phase in healing process in diabetes due to delayed increment of mast cells. The dysfunction of mast cells affects the angiogenesis in proliferative phase and vascular regression in the remodelling phase [48]. Tellechea et al, revealed in his experiment that mast cell degranulation was enhanced in the skin of humans and mice with diabetes that led to impaired healing process. Mast cell degranulation inhibitors like disodium cromoglycate, quercetin, and luteolin might be a potent drugs to improve wound healing in diabetes [49]. The RNA expression of MIF (Macrophage Migration Inhibitory Factor) genes deceases in diabeties, which is an important molecule in pro-inflammatory innate immune reactions. Studies reported that decreased level of MIF in diabetic wound might be responsible for impaired production of endothelial progenitor cells and healing process [51,52].

Heat shock proteins (HSPs) promotes wound healing by recruiting dermal fibroblasts, stimulate cell proliferation, differentiation of keratinocytes, decreases oxidative stress, alleviating actin microfilaments, assist endothelial cell migration, stimulate pro-collagen synthesis and protein homeostasis [43,53]. In diabetes, level of HSPs (HSP90, HSP70, HSP47 and HSP27) decreases along with their downstream molecules TLR4 and p38-MAPK [54] that might be responsible for impaired healing process.

3. Role of Growth factors in impaired wound healing

Normal wound healing cascade is well coordinated and synchronised by growth factors, different MMPs (Matrix metalloproteinase), cytokines, inflammatory cells, keratinocytes, fibroblasts and endothelial cells. Growth factors are biologically active polypeptides which are involved in all phase of healing process [55]. They promote the early inflammatory phase during the granulation phase of tissue formation. Compromised wounds frequently show defects in the type and amount of growth factor due to change of their expression, decreased production, decreased release, trapping and excessive

degradation [56]. Balance between matrix formation and matrix degradation characterizes ECM synthesis with optimum healing. Factors regulating ECM formation like VEGF [57], IGF-I, IGF-II [58], TGF-β[23] [59], KGF[24] [60], PDGF[25] [61], EGF[26] [62], FGF[27] [63,64], TNF- α and IL-6 are noticeably decreased in diabetic patients. Growth factors play a critical role in initiating and sustaining the different phases of wound healing (Fig. 4). Any alteration i.e. down-regulation of growth factor receptors and rapid degradation of growth factor leads to delayed wound healing in diabetics.

Platelet releases the PDGF that is a key serum mitogen and induces fibroblast proliferation, matrix production, and maturation of connective tissue [65]. PDGF is synthesized continuously in the wound milieu by macrophages which are major cell in the late inflammatory phase. PDGF works as a chemo-attractant for fibroblasts and inflammatory cells. It facilitates synthesis of glycosaminoglycans, proteoglycans and collagen. It acts as a key mediator in the migration and proliferation of fibroblasts, production of granulation tissue proteins and provisional ECM and angiogenesis during the healing process [66]. PDGF and its receptors expression is decreased in diabetic wounds, signifying its role in healing process [67]. Various clinical studies using PDGF have shown enhanced healing time [68].

bFGF[28] posses stimulatory effect on the growth and differentiated function of fibroblasts and on the proliferation of vascular smooth muscle cells, endothelial cells, extracellular matrix metabolism, growth, and movement of mesodermally derived cells. It increases the rate and degree of granulation tissue formation and stimulates healing process [69].

VEGF is one of the most potent known angiogenic cytokines in the skin, and the amount of VEGF present in a wound can notably impact healing and supports rate-limiting steps of vasculogenesis and angiogenesis. It mainly involves in deterioration of the extracellular matrix of existing vessels by proteases and causes migration and proliferation of capillary endothelial cells [70]. VEGF increases capillary density in diabetic wounds and improves the blood perfusion and metabolism in injured tissue. Restoration of blood flow to injured tissues facilitates oxygen and nutrients supply to support the growth and task of reparative cells which promotes wound healing. It is the main regulating factor in the revascularization and permeability of the wound site, and participates in the formation of the granulation tissue. Roles of VEGF be governed by activation of its receptors, first receptor VEGF receptor-1 activation leads to inflammation while activation of VEGF receptor-2 lead to angiogenesis [71]. The relatively low level of VEGF in local wound is due to diabetes responsible for impaired wound healing. Research studies found that abnormal patterns of VEGF receptors, decreased VEGF mRNA levels, increased VEGFR-1 level and decreased VEGFR-2 level is main reason for non-healing status of wounds [72].

Platelet releases EGF augmenting the epidermal cell, cell motility, cellular migration, mesenchymal regeneration, angiogenesis and cell proliferation after binding to the EGF receptor [73]. IGF-1 and IGF-2 are peptide that forms a complex Insulin-like growth factor (IGF). IGF-1 contributes in wound healing by participating in cell granulation and re-epithelisation, stimulating chemotaxis of endothelial cells and proliferation of keratinocytes and fibroblasts. However, in diabetes patients, expression of IGF-1 is decreased which may be the reason for cell granulation imperfection [74,75]. Its affinities are modulated by the pH of the wound environment [16].

The decreased levels of IGF-1 and TGF-β at the wound tissue were reported in both diabetic animals and human responsible for delayed wound healing process [76]. TGF-β recruits and promotes stimulation of inflammatory cells neutrophils, macrophages, lymphocytes, keratinocytes, fibroblasts and production of growth factors. These accelerate vascularisation, angiogenesis, and formation of ECM and hindered degradation of ECM [77]. The reduced concentration of TGF-β has been reported in wound healing in diabetic case [59]. Various studies demonstrated that MMP-encoding genes have a TGF-β1-dependent inhibitory element in the promoter region, which down-regulate the gene's expression. Decreased levels of TGF-β and increased expression of MMPs causes excessive degradation of the growth factors [78]. Along with MMP-encoding genes, Transcription factors like Smad-2, Smad-3 and Smad-4 also activate and repress TGF-β target genes. TGF-β1 activates the Smad-2 and 3 for production of collagen [79]. Decrease in level of TGF-β1 lead to increased recruitment of activated inflammatory cells causing delayed inflammatory phase to proliferation phase of healing process in DWs. High level of TGF-β3 was thought to be the reason for decreased level of TGF-β1 in diabetics [80] which lead to increased macrophage activity and decreased collagen synthesis. In diabetics, high glucose level augmented macrophage activity producing more reactive oxygen species leading to prolonged inflammatory phase [81]. Decreased level and expression of these growth factors lead to poor and prolonged wound healing process in diabetes.

4. Role of MMPs in impaired wound healing

Matrix metalloproteinase is a family of 26 zin. dependent endopeptidases that play crucial role in initial wound debridement, as well as in the phases of angiogenesis, epithelialization, and remodelling of extra cellular matrix [82]. Every matrix proteins like collagens, basement membrane collagens, proteoglycans, elastin, fibronectin are digested by MMPs. The gelatinase (MMP-2 and MMP-9) are two proteinases primarily responsible for breaking down of type IV collagen from the basic matrix. These are present as inactive zymogens that need removal of the pro domain for their activation. Activity of MMPs is regulated by complexation with TIMPs[29], which block contact to the active site. Balance between MMPs and TIMPs is required for a proper wound healing as supported by number of studies [83]. MMPs are involved in various stages of wound healing like cell migration by proteolysis of the ECM, in re-epithelialization by degradation of junctional proteins, in leukocyte invasion by creating a chemotactic gradient, in inflammation by processing of multiple cytokine either by inhibition or by activation [84]. In these enzymes MMP-1 is crucial for wound re-epithelialization, MMP-2 is significant during angiogenesis and prolonged matrix remodelling and MMP-3 is vital for normal wound contraction and in remodelling the basement membrane. While role of MMP-9 during healing is indistinct; it may be involved in separating keratinocyte from the basement membrane before migration and be used to assist matrix degradation by neutrophils and macrophages for the period of elimination of necrotic or damaged tissue [85]. Studies revealed that high levels of metalloproteases are a feature of diabetic wounds, and the MMP levels in chronic wound fluid are almost 60 times higher than acute wounds. This increased protease activity supports tissue destruction and inhibits normal repair processes [86]. One of the possible reasons behind this is high glucose concentrations that directly alter the level and expression of MMPs, decrease the expression of TIMPs via effects of persistently high levels of pro-inflammatory and pro-fibrotic cytokines due to increased activation and invasion of inflammatory cells, and indirectly affect MMPs by formation of advance glycation products [68]. These consequently abolish growth factors, receptors, and matrix proteins crucial for wound healing.

[23] Transforming growth factor β
[24] Keratinocyte growth factor
[25] Platelet derived growth factor
[26] Epidermal growth factor
[27] Fibroblast growth factor
[28] Basic fibroblast growth factor

[29] Tissue inhibitors of matrix metalloproteinase

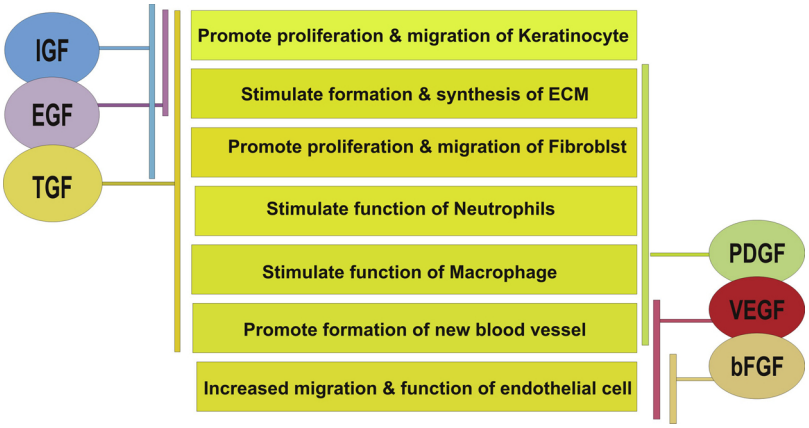

Fig. 4. Role of major Growth Factors on different cells and process involved in wound healing.

5. Molecular targets

Increased understanding of diabetes and its role in impaired wound healing at molecular level have broadened the wound research over recent years. These studies revealed that impaired wound healing in diabetics is due to unusual cellular expression of all participating cells and dys-regulation in the expression of cytokines, growth factors and various other molecular factors required for coordinating the normal healing process. As a result, chronic non-healing wounds are unable to step forward in synchrony and are checked mainly in the inflammatory phase. Numerous molecular factors/targets for management of diabetic wounds have been identified over the years. These management approaches are categorized on the basis of molecular targets which directly or indirectly modulates their activity.

The targets, which directly interact, include various growth factors (PDGF, TGF-α, EGF, VEGF, FGF, and KGF), autologous keratinocytes or autologous fibroblasts and stem cells. The role and importance of these targets were discussed in previous sections. Various agents might indirectly affect the molecular targets by up-regulated or down-regulated expression of growth factor, pro and anti inflammatory cytokines, MMP, nitrous oxide level, collagen synthesis /degradation and factors promoting angiogenesis depending on the specific target. These wound management approaches are classified on the basis of types of therapeutic agents used as drugs, growth factor, other approaches and stem cells and highlights of available clinical status for treatment of diabetic wounds are shown in Table 1. Table 1 also shown the molecular targets directly or indirectly involve in therapeutic approaches by formations or system or drug.

5.1. Natural product based treatment

Traditionally natural source obtained from different sources have been of prime importance to heal wound like turmeric, castor leaves, neem bark, rosemary, ginseng and many more. It has been reported that 70% of commercialized products contains plant based active ingredients, rest 20% are of mineral base and 10% are of animal based and more than 13,000 have been worked out particular to accelerate the process of wound healing. Plant actives which are involved in healing process include glycosides, steroids, saponins, resins, mucilage and flavonoids. Table 2 enlists most of the medicinally active plants which were demonstrated for their wound healing activity in diabetes and Table 3 depict the available marketed products used in management of diabetic wounds.

6. Clinical trials

Various clinical trials were on going to uncover a novel treatment approach for this worldwide health ailment. Tardivoe et al., 2014 performed a clinical trial using photodynamic therapy and result shown that rate of amputation in the photodynamic therapy group was 0.029 times the rate in the control group [87]. Park et al., 2018 performed a phase III multicenter, double-blind, randomized, placebo controlled trial to evaluate the efficacy and safety of a novel spray-applied growth factor therapy containing recombinant human epidermal growth factor (rhEGF) for the treatment of diabetic wounds. This group concluded that patients in the rhEGF treated group notably completed healing as compared to placebo group (73.2% vs 50.6%, respectively; $p = 0.001$). Also, healing velocity was found to be faster in the rhEGF treated group ($p = 0.029$) in spite of HbA1c levels. The rhEGF treated group had a shorter median time to 50% ulcer size reduction and shorter time to complete ulcer healing as compared to placebo group [54]. Asadi et al., 2017 performed a randomized, single-blind, placebo-controlled trial using low-intensity cathodal direct current. Results of this study suggested that on applying electric stimulation to ischemic ulcers have positive effects and promote healing by stimulate the release of HIF-1α and VEGF in the wound area [88]. Soleimani et al., 2017 performed a randomized, double-blind, placebo-controlled trial using flaxseed oil omega-3 fatty acids. This group concluded that on supplementation of omega-3 fatty acids for 12 weeks among diabetic wound patients had a favorable effects on parameters of ulcer size, indicators of insulin metabolism, plasma TAC, serum hs-CRP, and GSH levels [89]. Similar various clinical trials have been performed in recent years to promote healing in diabetic wound patients was described in Table 4.

7. Future therapeutic strategies

Diabetic wounds consequences from numerous risk factors including peripheral neuropathy, peripheral artery disease and foot ailments. In spite of the development in technologies such as bioengineered skin cells and the prevalent application of standard care in treating diabetic wounds, it has been reported that the occurrence of wound healing has remained at less than 50%. The research on diabetic wounds is proceeding hastily evident by new therapeutic approaches other than conventional such as single growth factor, dual growth factor, skin substitutes, cytokine stimulators, cytokine inhibitors, matrix metalloproteinase inhibitors, gene and stem cell therapy, extracellular matrix and angiogenesis stimulators. Future treatment approaches are at present under analysis for the treatment of diabetic wounds includes recombinant growth factors, platelet-rich plasma, Sphingosine 1-phosphate, Substance P, stem cell therapy, MMP inhibitors, shock-wave therapy, laser therapy and natural product based treatment. These approaches are the crucial need for a more realistic, secure and efficient therapy for diabetic wounds (Tables 1 and 2). The majority of these approaches are currently under investigation and their use has mostly been restricted to clinical trials.

Table 1
Therapeutic strategies explored management of wounds in diabetics.

Therapeutic agents	Delivery System and Route	Molecular Target	Outcome and Mechanism	Target tissue/ animal model	Reference
Growth factors					
PDGF/TGF-α	Topically/ Gel	PDGF and TGF-α	Promoting healing by increasing keratinocyte and fibroblast mitogen	Genetically diabetic mouse	[58]
basic fibroblast growth factor	PELA Nanofibres/ Topically	Fibroblast	Enhanced proliferation, migration, fibroblast adhesion, re-epithelization, angiogenesis, ECM restoration and remodelling	Diabetic rats	[90]
Human epidermal growth factor	Cream	EGF	Reduces the healing time	Diabetic foot ulcers	[91]
Recombinant epidermal growth factor	PLGA Microspheres	rhEGF	Increased healing by inducing fibroblasts proliferation and enhancing proliferating cell nuclear antigen in the epidermis	Diabetic ulcers	[92]
PDGF	Gel	PDGF	Increased angiogenesis, cell proliferation and epithelialization	Diabetic rats	[67]
basic fibroblast growth factor	collagen/gelatin sponge	———	Improve healing	Chronic skin ulcers	[93]
Platelet	Hyaluronic acid Gel	PGDF, TGF-α, VEGF	Enhance granulation tissue formation, re-epithelization and reduce pain	Cutaneous chronic wounds	[56]
Recombinant PDGF	Gel	PDGF	Increases reepithelialization, granulation tissue thickness, capillary density and improved healing by increased c-fos protein expression and ERK phosphorylation	Diabetic rats	[94]
Fusion protein (CBD-VEGF)	Collagen Domain	VEGF	Increases vascularisation and maintain VEGF activity	Diabetic rat model	[95]
Recombinant human acidic fibroblast growth factor	Chitosan crosslinked collagen sponge	FGF	Increases angiogenesis, collagen generation and dermal cell proliferation	Diabetic rats	[96]
Recombinant epidermal growth factor	Poly-epsilon-caprolactone and poly-ethyleneglycol Nanofibres	EGF	Promotes proliferation and expression of keratinocytes	Diabetic ulcers	[97]
Arginine and Epidermal growth factor	Hyaluronic acid sponge	EGF	Decreased wound size by increasing the epithelization		[98]
bFGF	Collagen-gelatin sponge	FGF	Accelerate ECM formation and angiogenesis	Diabetic mouse model	[99]
Keratinocytes growth factor	Chimeric Nanoparticles	KGF	Increased healing by enhancing reepithelialization and granulation tissue formation	Chronic wounds	[100]
plasmid bFGF	Poly(Ethylene Imine) electrospun Fibers	FGF	Increased healing by enhanced collagen synthesis, maturation and reepithelialization	Diabetic skin wound	[101]
rhEGF	Dextrin conjugated Topically	———	Accelerated wound closure, neo-dermal tissue formation, increased granulation tissue deposition and angiogenesis	(Db/db) diabetic mouse	[73]
Dual growth factor	Poly(lactic-co-glycolic acid) nanoparticles in chitosan nanofiber system	VEGF, PDGF-BB	Accelerated the healing process by increasing angiogenesis, re-epithelialization and granulation tissue formation	———	[102]
PDGF	Collagen Chitosan hydrogel/ Topically	———	Increased collagen biosynthesis and by reducing reactive oxygen species	Cutaneous wound healing	[103]
PDGF-BB	Carboxymethyl cellulose Hydrogel/ Topically	———	Accelerated healing by enhanced granulation tissue formation and angiogenesis	Genetically diabetic mice	[104]
bFGF	Chitosan film/ Topically	FGF	Reduced wound area and promoted healing by increasing ECM formation	Genetically diabetic mice	[105]
Recombinant human Epidermal growth factor	Polyurethane foam/ Topically	———	Accelerated healing by increasing contraction rate, re-epithelialization and collagen deposition	Diabetic wounds	[106]
VEGF	Poly(lactic-co-glycolic acid) nanoparticle	VEGF Receptor -2	Enhanced proliferation and migration of keratinocytes and upregulated the expression of VEGFR2 at mRNA level	Non-diabetic and diabetic wounds	[107]
Synthetic drugs					
Pravastatin	Subcutaneous sponges	eNOS expression	Improve wound breaking strengths, hydroxyproline accumulation by up-regulation of eNOS and NO expression	Diabetic wound	[108]
Azelnidipine	Solution/Orally	eNOS	Accelerated healing by stimulating NO production and enhancing histologic processes	Skin Wound in Diabetic Rats	[109]
AL–CS–PGA hydrogel	Hydrogel	Collagen	Increases healing by collagen regeneration and epithelialization	Diabetic rats	[110]
Atorvastatin gel	Carbopol Hydrogel	———	Increased healing with closure and epithelisation within 7 days	Diabetic rats	[111]
Erythropoietin	Cream	VEGF	Decreased wound closure time, increased VEGF and hydroxyproline and microvascular density	Diabetic rats	[112]
Pentoxifylline	Cream	MMPs and TIMP-1	Accelerates healing by decreasing MMPs expression and increased TIMP-1 expression	Diabetic rats	[113]

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Table 1 (*continued*)

Therapeutic agents	Delivery System and Route	Molecular Target	Outcome and Mechanism	Target tissue/ animal model	Reference
Deferoxamine	Intra-peritoneally	HIF-1α, SDF-1α, VEGF	Increased neovascularisation and healing by promoting endothelial tube formation and cell proliferation through up-regulation of HIF-1α	Diabetic rats	[114]
	Topically	———	Increased neovascularisation and healing by decreasing mRNA expression and protein levels of TNF-α, MMP-9 and IL-1β	Diabetic rats	[115]
Substance P	I.V.	endothelial cell adhesion molecules or IL-8	Increases early leukocyte and macrophage density in healing and promoting cutaneous wound repair	Diabetic murine wounds	[116]
	Topical application	———	Decreased levels of TNF-α, IL-1β and MMP-9 and increase IL-10 levels and increased the expressions of VEGF, TGF-b, SDF-1α, HO-1 and e-NOS.	Diabetic rat	[117]
			Reverses the proinflammatory state in diabetic wound and modulate activation of macrophage and improve healing	Diabetic skin wounds	[118]
Propranolol	Solution Orally	VEGF, TGF-β, IL-8, MMP-9	Reduces inflammatory cell and MMP-9 levels and increases cell proliferation, mast cell number, collagen deposition, blood vessel density, and nitric oxide level	Diabetic rats	[119]
Glucophage (metformin)	nanofibrous collagen/PLGA membrane	MMP-9	Faster healing by increased re-epithelialization and collagen I synthesis by down-regulating MMP-9	Diabetic wound	[120]
Novel nano-insulin	Silver nanoparticles Coated with Insulin	IL-6, TNF-α, IL-10	Regulation of balance among IL-6, TNF-α and IL-10 at the wound site to promote faster wound remodeling	Diabetic rats	[121]
GW501516	Polymer Microparticle/	peroxisome proliferator-activated receptor	Reduced the oxidative wound micro-environment to accelerate healing	Diabetic wound	[122]
MK0626	Dipeptidyl peptidase-4 inhibitor/ Oral	HIF-1α / SDF-1	Significantly improved healing, angiogenesis, and endogenous progenitor cell recruitment.	Diabetic mice	[123]
Poly (caprolactone) /gelatin nanofibrous composite scaffold	Conducive Poly (caprolactone) /gelatin nanofibrous composite scaffold containing silicate-based bioceramic particles	Epithelial-to-mesenchymal transition and endothelial mesenchymal transformation pathway	Improve diabetic wound healing by releasing Si ions and ano-fibrous structure	Diabetic mice	[124]
Adenine	Ointment	AMP-activated protein Kinase, PPARδ	Increasing the healing by increasing angiogenic related protein PPARδ and decrease the AGE receptors.	Diabetic mice	[125]
Bee venom	Subcutaneous injection	Nrf2, Ang-1 and Tie-2 signaling	Enhanced wound by rising collagen and BD-2 expression and reinstate the levels of Ang-1 and Nrf2 and Tie-2 downstream signaling	Diabetic mice	[126]
Curcumin	Composite graft with Cytomodulin coupled porous PLGA microparticles	——	Better and faster wound healing with regenerating a skin of higher tensile strength.	Diabetic rats	[127]
Other approaches					
Sphingosine 1-phosphate	Subcutaneous	EDGs	Accelerates healing by increased vascular formation within the granulation tissue	Diabetic mice	[128]
Adiponectin		TGF-β	Restrain proliferation and differentiation of keratinocytes, and regulates the expression of TGF-β	Diabetic wound	[129]
Neurotensin	5-methyl pyrrolidinone Chitosan Dressing	TNF-α, IL- 1β, collagen expression	Reduced inflammatory status, improve healing, re-epithelialization by decreasing inflammatory infiltrate and increasing fibroblast migration and collagen deposition	Diabetic wound	[130,131]
	Collagen dressings	TNF-α, IL-1β	Reduced inflammatory cytokine TNF-α, IL-1β and MMPs, increased fibroblasts migration and collagen expression and deposition	Diabetic mice	
Broad-spectrum MMP inhibitor	Sepharose resin, Topically	MMP and TIMP	Accelerate healing, re-epithelialization and inhibit MMP-9 activity	Diabetic wound	[28]
Hyaluronic acid	Solution, I.P.	TGF-β	Improved healing by increasing skin remodelling proteins, TGF-β and transglutaminase-II	Genetically diabetic mice	[132]
HoxD3 plasmid DNA	Methylcellulose Film	HoxD3, Col1A1 and β3-integrin	Significant acceleration of wound closure by increasing mRNA expression of HoxD3, Col1A1 and β3-integrin leading to enhanced angiogenesis and collagen deposition	Diabetic mice	[133]
Human Amniotic fluid Proteome	———	———	Accelerates healing by activating mitosis and angiogenesis	Diabetes-impaired wound	[134]

(*continued on next page*)

Table 1 (*continued*)

Therapeutic agents	Delivery System and Route	Molecular Target	Outcome and Mechanism	Target tissue/ animal model	Reference
Angiopoietin-like 4	Topical	Nitric Oxide	Increases diabetes induce wound healing via increasing nitric oxide production accelerated reepithelialization and improving angiogenesis	Diabetic mice and human skin tissue	[41]
Stem cells					
Adipose tissue-derived Mesenchymal Stem Cells	Intra-dermally	VEGF, HGF	Enhances healing by anti-inflammatory and anti-apoptotic effects	Diabetic rats	[135]
Autologous Keratinocytes or Autologous Fibroblasts	Cell suspension	Fibroblast, Keratinocyte	Accelerate healing by enhancing re-epithelialization rate	Diabetic porcine wound	[136]
Allogenous skin fibroblasts	Cell suspension	Fibroblast	Promote healing by increasing re-epithelialization, fibroblasts and angiogenesis	Diabetic sheep	[137]
BM derived Mesenchymal Stem Cells	Subcutaneously Cell suspension	———	Stimulate healing by increasing production of cytokines and/or by stimulation of endogenous resident cells	Murine and human cutaneous wounds	[138]
		EGF, VEGF, Prolyl4-hydroxylase, Ki-67 expression	Enhances healing by reduction in topical pro-inflammatory reaction and increases VEGF	Diabetic rats	[139]
Mesenchymal Stem cells	————	————	Promotes healing by enhancing angiogenesis	Diabetic wound	[140]
	Electrospun Collagen Scaffold	Fibroblast	Enhancing healing by promoting fibroblast migration and proliferation	Diabetic mice	[141]
Topical embryonic stem cells	Topical injection	EGF, VEGF	Accelerated healing by stimulating epidermal regeneration, granulation tissue formation and angiogenesis via increasing EGF, VEGF and fibronectin	Diabetic rats	[142]
Amniotic Mesenchymal Stem Cells	Injection	angiogenic factors	Promotes healing by up-regulation of angiogenic factors, IGF-1, EGF and IL-8 and enhanced engraftment/ differentiation capabilities	Diabetic NOD/SCID mice	[143]
Placenta mesenchymal stem cell	Intradermal injection	Pro-angiogenic molecules	Accelerates healing by stimulating vascular regeneration	Diabetic Goto-Kakizaki rats	[144]
BM-derived SPCs	Topical	————	Improves healing via indirect mechanisms that enhanced angiogenesis	Diabetic mice	[145]
Adipose tissue-derived stromal cells	Atelocollagen matrix	————	Accelerating healing by increasing granulation tissue formation, epithelium, and capillaries	Db/db mice	[146]
Dermal sheath derived Mesenchymal Stromal cells	———	IL-6, IL -8 and growth-related oncogene	Enhanced keratinocytes, fibroblasts proliferation and endothelial cells in vitro and decreases healing time	Diabetic wound	[147]
Umbilical cord blood-derived hematopoietic stem cells ($CD34^+$cells)	3D fibrin gel with $CD34^+$-derived endothelial cells	IL-17, IL-10, ERK1/2 patway	Reduces the inflammatory reaction and enhances neovascularization	Diabetic mice	[148]
Adipose-derived stem cells	Injectable hydrogel system	CD11b, TNF α, IL-1	Accelerated healing by inhibiting inflammation and promoting angiogenesis and re-epithelialization.	Humanized excisional wound model	[149]
Adipose-derived stem cells, Endothelial-differentiated stem cells	Injection	——	Increase in the % of wound closure rates in cell-based treatments.	Diabetic swine	[150]
Human umbilical cord blood–derived mesenchymal stromal cells	Transplantation	Collagen and (TGF)-β	Improved the healing by increasing collagen synthesis and angiogenesis.	Diabetic Mice	[151]

Table 2
Natural product based treatment for diabetic wounds.

Natural products	Outcome with possible mechanism	Animal model	Ref.
Rosmarinus officinalis L. *Family: Lamiaceae*	Reduced inflammation, debridement, increased contraction, epidermal regeneration and organization	alloxan induced-diabetic mice	[152]
Curculigo orchioides G. *Family: Hypoxidaceae*	Improve healing by increasing superoxide dismutase, nitric oxide and decreased lipid peroxidation	Streptozotocin induced diabetic mice	[153]
Melilotus officinalis (L.) Pall. *Family: Fabaceae*	Induces micro-vascularisation and Anti-inflammatory activity	Diabetic patients	[154]
Rehmanniae Libosch. ex Fisch. & C.A. Mey. *Family: Orobanchaceae*	Improved healing by enhancing tissue regeneration, angiogenesis and inflammation control	Streptozotocin-induced diabetic rat	[155]
Curcumin *Curcuma longa* L.	Increased wound closure rate by reduced inflammatory induction and antioxidant activity	Streptozotocin induced diabetic mice model	[156]
Family: Zingiberaceae	Improved healing by increasing granulation tissue, fibroblasts proliferation and collagen deposition	Streptozotocin induced diabetic rats	[157]
	Enhanced healing by accelerated neovasculogenesis, increased expressions of VEGF, TGF-β, hypoxia-inducible growth factor-1α, stromal cell-derived growth factor-1α, and heme oxygenase-1	Streptozotocin induced diabetic rats	[158]
Martynia annua L. *Family: Martyniaceae*	Enhanced healing by free-radical scavenging activity of the flavonoids and luteolin	Streptozotocin induced diabetic rats	[159]
Genistein Genista tinctoria L. Family: Fabaceae	Improved healing and angiogenesis by suppression of FoxO1, iNOS activity and oxidative stress	STZ-induced type 1 diabetic mice	[160]
Lithospermun erythrorhison Siebold & Zucc. *Family: Boraginaceae*	Decreased vascular permeability, increased granulation tissue formation	Diabetic mice	[161]
Astragalus membranaceus (Fisch.) *Family: Fabaceae,* *Rehmannia glutinosa (Gaertn.) Steud.* *Family: Orobanchaceae*	Increased healing and post-ischemic neovascularization by augmenting blood vessel density, VEGF and eNOS expression, and attenuate oxidative stress	STZ induced rat with hindlimb ischemia model	[162]
Astragalus membranaceus (Fisch.) *Family: Fabaceae,* *Rehmanniae Libosch. ex Fisch. & C.A. Mey.* *Family: Orobanchaceae*	Enhanced healing by increased tissue regeneration, promoting angiogenesis and inhibiting inflammation	Streptozotocin-induced diabetic rat	[163]
Annona squamosa L. *Family: Annonaceae*	Enhanced epithelialization rate, cellular proliferation and collagen synthesis	Streptozotocin-induced diabetic rat	[164]
Nicotine Nicotiana tabacum L. Family: Solanaceae	Accelerated healing and angiogenesis	Streptozotocin induced diabetic mice	[165]
Allium sativum L. *Family: Amaryllidaceae*	Improve healing in diabetes	Alloxan induced diabetic rats	[166]
Naringin	Enhanced healing by inducing angiogenesis and down-regulate the expression of TNF-α, IL-1β and IL-6 and upregulate the expression of IFG-1, VEGF and TGF-b	Streptozotocin-induced diabetic rat	[167]
Aloe vera (L.) Burm.f. *Family: Asphodelaceae*	Accelerated healing	Streptozotocin-induced diabetic rat	[168]
Sparassis crispa (Wulfen) Fr. *Family: Sparassidaceae*	Improve healing by promoting migration of macrophages, fibroblasts, and synthesis of type I collagen.	streptozotocin induced diabetic rats	[169]
Honey Apis mellifera L. Family: Apidae	Promotes epithelisation	Human patients	[170]
Honey with hydroalginate	Improve wound healing	Human patients	[171]
Astragulus polysaccharide-loaded fibrous mats	Accelerated healing by restoration of microcirculation and promoted angiogenesis	Streptozotocin-induced diabetic rat	[172]
Angelica sinensis (Oliv.) Diels, *Family: Apiaceae* *Astragalus membranaceus (Fisch.)* *Family: Fabaceae,* *Angelica dahurica Fisch.ex Hoffm.,* *Family: Apiaceae and Gleditsia sinensis Lam.* *Family: Fabaceae*	Improve healing by reduced neutrophil infiltration and macrophage accumulation, enhanced angiogenesis, and increased collagen deposition	Streptozotocin-induced diabetic rat	[173]
Bee venom	Enhanced wound closure by increasing collagen production and reinstating the levels of inflammatory cytokines by acting on ATF-3 and iNOS	Type I diabetic mouse model	[33]
Camel milk Peptide	Restore the normal redox status and activate the inflammatory cascade and stimulates healing	Streptozotocin-induced diabetic rat	[52]
Whey Protein	Improves healing by increased glutathione synthesis and cellular antioxidant defence	Streptozotocin-induced diabetic mice	[37]
	Improved healing by Up-regulation of Hsp72 and keratin16	Streptozotocin-induced diabetic rat	[174]
	Enhanced collagen deposition, restored the activation of STAT3, Akt and NF-κB	Streptozotocin-induced diabetic mice	[175]
Propolis	Enhance healing by increasing collagen production via TGF β1 and smad2, 3 signaling	Streptozotocin-induced diabetic mice	[79]

Table 3
Marketed Products for rapid wound healing in diabetes.

Product	Composed of	company
Apligraf (Graftskin)	Bovine collagen and living fibroblasts and keratinocytes	Novartis, Switzerland
Dermagraft	Cryopreserved human fibroblasts-derived dermal substitute	Shireplc, USA
Becaplermin (Regranex)	Platelet Derived Growth Factor-BB	Smith & Nephew, Inc., USA
Bilayered living human skin equivalent	Cultured keratinocytes on the fibroblast-populated collagen lattice	
Angipars	*Melilotus officinalis*	Endocrinology and Metabolism Research Institute, Iran
Ampucare	*Azadirachta indica* and *Curcuma longa*	Venus Remedies Ltd., India
Fiblast Spray (Trafermin)	Recombinant bovine bFGF	Kaken Pharmaceutical Co.,Ltd.
MediHoney	80% active *Leptospermum* honey with colloidal alginate	Derma Sciences, Inc., USA
rHuHSP90a-115	Topical protein drug	
Woulgan® biogel (in clinical trial)	Biotec Pharmacon's soluble yeast beta-glucan (SBG)	Biotec Pharmacon, Norway

Table 4
List of clinical trials studies on diabetic wound.

S. No.	Study design	Drugs/ Methods	Result	References
1.	Randomized phase III Clinical Trials	Topical betulin gel	Accelerates re-epithelialization of partial thickness wounds	[176]
2.	Randomized Clinical Trials	Honey dressing	In treated group, microbial clearance, and healing area were notably higher than control groups.	[177]
3.	Randomized Clinical Trials	Royal Jelly	Healing area, healing rate and time not showing any change with placebo treated group.	[178]
4.	Randomized Clinical Trials	Manuka honey-impregnated dressing	Healing time of treated group was considerably lower than control group. And % of ulcers healed did not change significantly between groups	[179]
5.	Randomized, Double-blind	Dragon's blood cream	Dragon's blood cream significantly improves healing duration.	[180]
6.	Single-blinded randomized controlled	Extracorporeal Shock wave therapy	Noteworthy decrease in wound size and median time requisite for ulcer healing.	[181]
7.	Single-arm clinical trial	Autologous platelet-rich plasma gel	Wound area significantly decreased in treated group as compared to control.	[182]
8.	Randomized Controlled trial	LeucoPatch system	LeucoPatch treated group, 34% ulcers healed within 20 weeks as compared to 22% ulcers in the standard care group.	[183]
9.	Randomized Controlled trial	Negative pressure wound therapy	Reduces the granulation time of by 40% in diabetic wounds as compared to standard wound dressing.	[184]

8. Conclusion

There has been exponential growth of research in the field of diabetic wound management over the past years. Impaired wound healing is common impediment of diabetes that has potentially devastating consequences on suffering patients. Numerous factors contribute to impaired healing in diabetes as suggested by various researches. Significant developments have been made on various new therapeutic approaches and products in management of wound healing in diabetes. Approaches involving the growth factor, dual growth factors, various cytokines modulators, anti-inflammatory drugs, MMP inhibitors, angiogenesis stimulator, ECM stimulators, stem cells, and various natural based products have been evaluated with limited achievement. Recent studies based on combinational approach have overpowered conventional approaches. It presents a hope for the researchers to go through the new advancement in the designing of novel carrier along with understanding basic approach. Combination approaches can be an important area for future research in management of compromised wounds. Thus, contributing towards accelerated healing of diabetic wounds. Strong research is needed to recognize different agents that could act at different phase of wound healing in diabetes. Getting better clinical methodologies and system can be of assistance in recognizing the extent of healing.

Declaration of interest

The authors report no declarations of interest.

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References

[1] World Health Organization, Facts and Figures About Diabetes, Available at: (2014) http://www.who.int/mediacentre/factsheets/fs312/en/.2014.
[2] World Health Organization, Facts and Figures About Diabetes, Available at: (2013) 2013 http://www.who.int/diabetes/facts/en/.
[3] V. Vijayakumar, S.K. Samal, S. Mohanty, S.K. Nayak, Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management, Biomacromolecules (2018), https://doi.org/10.1016/j.ijbiomac.2018.10.120.
[4] A. Mohandas, B.S. Anisha, K.P. Chennazhi, R. Jayakumar, Chitosan-hyaluronic acid/VEGF loaded fibrin nanoparticles composite sponges for enhancing angiogenesis in wounds, Colloids Surf.: B Biointerface 27 (2015) 105–113.
[5] B.S. Anisha, R. Biswas, K.P. Chennazhi, R. Jayakumar, Chitosan-hyaluronic acid/nano silver composite sponges for drug resistant bacteria infected diabetic wounds, Int. J. Biol. Macromol. 62 (2013) 310–320.
[6] A. Komarcevic, The modern approach to wound treatment, Med. Pregl. 53 (2000) 363–368.
[7] A. Sharp, J. Clark, Diabetes and its impact on wound healing, Nurs. Stand. 25 (2011) 41–47.
[8] D. Singh, M. Singh, S. Saraf, S. Saraf, Development of delivery cargoes for debriding enzymes effective in wound healing, Trends Appl. Sci. Res. 6 (2011) 863–876.
[9] M.R. Singh, S. Saraf, A. Vyas, V. Jain, D. Singh, Innovative approaches in wound healing: trajectory and advances, Artif. Cell Nanomed. Biotechnol. 41 (2013) 202–212.
[10] A. Alavi, R.G. Sibbald, D. Mayer, L. Goodman, M. Botros, D.G. Armstrong, et al., Dabetic foot ulcers part I. Pathophysiology and prevention, J. Am. Acad. Dermatol. (2014) 1e1–1e16.
[11] H. Galkowska, U. Wojewodzka, W.L. Olszewski, Chemokines, cytokines, and growth factors in keratinocytes and dermal endothelial cells in the margin of chronic diabetic foot ulcers, Wound Repair Regen. 14 (2006) 558–565.
[12] K.V. Kavitha, S. Tiwari, V.B. Purandare, S. Khedkar, S.S. Bhosale, A.G. Unnikrishnan, Choice of wound care in diabetic foot ulcer: a practical approach, World J. Diabetes 5 (2014) 546–556.
[13] S.B. Mallik, B.S. Jayashree, R.R. Shenoy, Epigenetic modulation of macrophage polarization- perspectives in diabetic wounds, J. Diabetes Complicat. (2018),

https://doi.org/10.1016/j.jdiacomp.2018.01.015.
[14] K. Maruyama, et al., Decreased macrophage number and activation lead to reduced lymphatic vessel formation and contribute to impaired diabetic wound healing, Am. J. Pathol. 170 (2007) 1178–1191.
[15] S. Okizaki, Y. Ito, K. Hosono, K. Oba, H. Ohkubo, H. Amano, et al., Suppressed recruitment of alternatively activated macrophages reduces TGF-β1 and impairs wound healing in streptozotocin induced diabetic mice, Biomed. Pharmacother. 70 (2015) 317–325.
[16] M.A.M. Loots, S.B. Kenter, F.L. Au, W.J.M.Y. Galen, E. Middelkoop, J.D. Bos, J.R. Mekkes, 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 (1991) 153–160.
[17] H. Brem, M. Tomic-Canic, Cellular and molecular basis of wound healing in diabetes, J. Clin. Invest. 117 (2007) 1219–1222.
[18] C. Schurmann, I. Goren, A. Linke, J. Pfeilschifter, S. Frank, 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 (2014) 195–200.
[19] J. Moura, E. Borsheim, E. Carvalho, The role of MicroRNAs in diabetic complications-special emphasis on wound healing, Genes (Basel) 29 (2014) 926–956.
[20] S. Biswas, et al., 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 (2010) 6976–6981.
[21] Y.C. Chan, S. Roy, S. Khanna, C.K. Sen, Downregulation of endothelial microRNA-200b supports cutaneous wound angiogenesis by desilencing GATA binding protein 2 and vascular endothelial growth factor receptor 2, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1372–1382.
[22] S. Bhattacharya, R. Aggarwal, V.P. Singh, S. Ramachandran, M. Datta, Downregulation of miRNAs during delayed wound healing in diabetes: role of dicer, Mol. Med. 2 (2015) 847–860.
[23] B. Icli, C.S. Nabzdyk, J.L. Hernandez, M. Cahill, M.E. Auster, et al., Regulation of impaired angiogenesis in diabetic dermal wound healing by microRNA-26a, J. Mol. Cell Cardiol. 91 (2016) 151–159.
[24] Z. Li, S. Guo, F. Yao, Y. Zhang, T. Li, Increased ratio of serum matrix metalloproteinase-9 against TIMP-1 predicts poor wound healing in diabetic foot ulcers, J. Diabetes Complicat. 27 (2013) 380–382.
[25] L. Pradhan, X. Cai, S. Wu, N.D. Andersen, M. Martin, J. Malek, et al., Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing, J. Surg. Res. 167 (2011) 336–342.
[26] C.J.N. Verkleij, J.J.T.H. Roelofs, S.R. Havik, J.C.M. Meijers, P.F. Marx, The role of thrombin-activatable fibrinolysis inhibitor in diabetic wound healing, Thromb. Res. 126 (2010) 442–446.
[27] N. Nass, K. Vogel, B. Hofmann, P. Presek, R.E. Silber, A. Simm, Glycation of PDGF results in decreased biological activity, Int. J. Biochem. Cell Biol. 2010 (42) (2010) 749–754.
[28] M. Gooyit, Z. Peng, W.R. Wolter, H. Pi, D. Ding, D. Hesek, M. Lee, et al., A chemical biological strategy to facilitate diabetic wound healing, ACS Chem. Biol. 9 (2014) 105–110.
[29] M. Brownlee, The patho-biology of diabetic complications: a unifying mechanism, Diabetes 54 (2005) 1615–1625.
[30] S.K. Niture, A.K. Jaiswal, Inhibitor of Nrf2 (INrf2 or Keap1) protein degrades Bcl-xL via phosphoglycerate mutase 5 and controls cellular apoptosis, J. Biol. Chem. 286 (2014) 44542–44556.
[31] M. Long, M. Rojo de la Vega, Q. Wen, M. Bharara, T. Jiang, R. Zhang, S. Zhou, et al., An essential role of NRF2 in diabetic wound healing, Diabetes 65 (2016) 780–793.
[32] S. Nakagomi, Y. Suzuki, K. Namikawa, S. Kiryu-Seo, H. Kiyama, Expression of theactivating transcription factor 3 prevents c-Jun N-terminal kinase-induced neuronal death by promoting heat shock protein 27 expression and Akt activation, J. Neurosci. 23 (2003) 5187–5196.
[33] G. Badr, W.N. Hozzein, H.M.S. Eldien, B.M. Badr, O. Garraud, Bee venom accelerates wound healing in diabetic mice by suppressing activating transcription factor-3 (ATF-3) and inducible nitric oxide synthase (iNOS)-mediated oxidative stress and recruiting bone marrow derived endothelial progenitor cells, J. Cell. Physiol. 9999 (2016) 1–13.
[34] G. Badr, Camel whey protein enhances diabetic wound healing in a streptozotocin-induced diabetic mouse model: the critical role of β-Defensin-1, -2 and -3, Lipids Health Dis. 12 (2013) 46–57.
[35] O. Dewald, P. Zymek, K. Winkelmann, A. Koerting, G. Ren, et al., CCL2/Monocyte chemoattractant Protein-1 regulates inflammatory responses critical to healing myocardial infarcts, Circ. Res. 96 (2005) 881–889.
[36] Y. Ishida, J.L. Gao, P.M. Murphy, Chemokine receptor CX3CR1 mediates skin wound healing by promoting macrophage and fibroblast accumulation and function, J. Immunol. 180 (2008) 569–579.
[37] G. Badr, Supplementation with undenatured whey protein during diabetes mellitus improves the healing and closure of diabetic wounds through the rescue of functional long-lived wound macrophages, Cell. Physiol. Biochem. 29 (2012) 571–582.
[38] W. Clayton, A.Tom Elasy, A review of the patophysiology, classification, and treatment of foot ulcers in diabetic patients, Clin. Diabetes 27 (2009) 52–53.
[39] H. Huang, W. Cui, W. Qiu, M. Zhu, R. Zhao, D. Zeng, et al., Impaired wound healing results from the dysfunction of the Akt/mTOR pathway in diabetic rats, J. Dermatol. Sci. (2015), https://doi.org/10.1016/j.jdermsci.2015.06.002.
[40] M.H.M. Lima, A.M. Caricilli, L.L. de Abreu, E.P. Araujo, F.F. Pelegrinelli, et al., Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial, PLoS One 7 (2012) e36974.
[41] H.C. Chong, J.S.K. Chan, C.Q. Goh, N.V. Gounko, X. Wang, S. Foo, et al., Angiopoietin-like 4 stimulates STAT3-mediated iNOS expression and enhances angiogenesis to accelerate wound healing in diabetic mice, Mol. Ther. 22 (9) (2014) 1593–1604.
[42] A.Y. Peleg, T. Weerarathna, J.S. McCarthy, T.M. Davis, Common infections in diabetes: pathogenesis, management and relationship to glycaemic control, Diabetes Metab. Res. Rev. 23 (2007) 13.
[43] K. Singh, N.K. Agrawal, S.K. Gupta, G. Mohan, S. Chaturvedi, K. Singh, Decreased expression of heat shock proteins may lead to compromised wound healing in type 2 diabetes mellitus patients, J. Diabetes Complicat. 29 (2015) 578–588.
[44] K. Singh, N.K. Agrawal, S.K. Gupta, G. Mohan, S. Chaturvedi, K. Singh, Genetic and epigenetic alterations in Toll like receptor 2 and wound healing impairment in type 2 diabetes patients, J. Diabetes Complicat. 29 (2015) 222–229.
[45] K. Smith, A. Collier, E.M. Townsend, L.E. O'Donnell, A.M. Bal, J. Butcher, et al., One step closer to understanding the role of bacteria in diabetic foot ulcers: characterising the microbiome of ulcers, BMC Microbiol. 16 (2016) 54–66.
[46] J. Moura, J. Rodrigues, M. Gonçalves, C. Amaral, M. Lima, E. Carvalho, Impaired T-cell differentiation in diabetic foot ulceration, Cell Mol. Immunol. (2016) 21.
[47] Y. Abiko, D. Selimovic, The mechanism of protracted wound healing on oral mucosa in diabetes, Bosnian J. Basic Med. Sci. 10 (2010) 186–191.
[48] Y. Nishikori, H. Okunishi, N. Shiota, The role of mast cells in cutaneous wound healing in streptozotocin-induced diabetic mice, Arch. Dermatol. Res. 306 (2014) 823–835.
[49] A. Tellechea, E.C. Leal, A. Kafanas, M.E. Auster, S. Kuchibhotla, Y. Ostrovsky, F. Tecilazich, D. Baltzis, et al., Mast Cells Regulate Wound Healing in Diabetes, Diabetes 65 (2016) 2006–2019.
[50] D. Bevan, E. Gherardi, T.P. Fan, D. Edwards, R. Warn, Diverse and potent activities of HGF/SF in skin wound repair, J. Pathol. 203 (2004) 831–838.
[51] G. Grieb, D. Simons, L. Eckert, M. Hemmrich, G. Steffens, J. Bernhagen, et al., Levels of macrophage migration inhibitory factor and glucocorticoids in chronic wound patients and their potential interactions with impaired wound endothelial progenitor cell migration, Wound Repair Regen. 20 (2012) 707–714.
[52] H. Ebaid, B. Abdel-salam, I. Hassan, J. Al-Tamimi, A. Metwalli, I. Alhazza, Camel milk peptide improves wound healing in diabetic rats by orchestrating the redox status and immune response, Lipids Health Dis. 14 (2015) 132–142.
[53] M. Luong, Y. Zhang, T. Chamberlain, T. Zhou, J.F. Wright, K. Dower, et al., Stimulation of TLR4 by recombinant HSP70 requires structural integrity of the HSP70 protein itself, J. Inflamm. 9 (2012) 11.
[54] K.W. Park, S.H. Han, J.P. Hong, S. Han, D. Lee, B.S. Kim, J.H. Ahn, J.W. Lee, Topical epidermal growth factor spray for the treatment of chronic diabetic foot ulcers: a phase III multicenter, double-blind, randomized, placebo controlled trial, Diabetes Res. Clin. Pract. 142 (2018) 335–344.
[55] S. Barrientos, O. Stojadinovic, M.S. Golinko, H. Brem, M. TomicCanic, Growth factors and cytokines in wound healing, Wound Repair Regen. 16 (2008) 585–601.
[56] G. Crovetti, G. Martinelli, M. Issi, M. Barone, M. Guizzardi, et al., Platelet gel for healing cutaneous chronic wounds, Transfus. Apher. Sci. 30 (2004) 145–151.
[57] S. Frank, G. Hubner, G. Breier, M.T. Longaker, D.G. Greenhalgh, S. Wener, Regulation of vascular endothelial growth factor expression in cultured keratinocytes. Implications for normal and impaired wound healing, J. Biol. Chem. 270 (1995) 12607–12613.
[58] R.L. Brown, M.P. Breeden, D.G. Greenhalgh, PDGF and TGFα act synergistically to improve wound healing in genetically diabetic mouse, J. Surg. Res. 56 (1994) 62–70.
[59] M.S. Bitar, Z.N. Labbad, Transforming growth factor-β and insulin-like growth factor I in relation to diabetes-induced impairment of wound healing, J. Surg. Res. 6 (1996) 113–119.
[60] S. Werner, M. Breeden, G. Hubner, et al., Induction of keratinocyte growth factor expression is reduced and delayed during wound healing in the genetically diabetic mouse, J. Invest. Dermatol. 103 (1994) 469–473.
[61] H.D. Beer, M.T. Longaker, S. Werner, Reduced expression of PDGF and PDGF receptors during impaired wound healing, J. Invest. Dermatol. 109 (1997) 132–138.
[62] N.L. Burstein, Growth factor effects on corneal wound healing, J. Ocular Pharmacol. Ther. 3 (1987) 263–277, https://doi.org/10.1089/jop.1987.3.263.
[63] R. Hosokawa, K. Kikuzaki, T. Kimoto, T. Matsuura, D. Chiba, M. Wadamoto, et al., 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 (2000) 345–353.
[64] M.H. Parkar, L. Kuru, M. Giouzeli, I. Olsen, Expression of growth-factor receptors in normal and regenerating human periodontal cells, Arch. Oral Biol. 46 (2001) 275–284.
[65] D.G. Greenhalgh, K.H. Sprugel, M.J. Murray, R. Ross, PDGF and FGF stimulate wound healing in the genetically diabetic mouse, Am. J. Pathol. 136 (1990) 1235–1246.
[66] D.L. Doxey, M.C. Ng, R.E. Dill, A.M. Iacopino, Platelet-derived growth factor levels in wounds of diabetic rats, Life Sci. 57 (1995) 1111–1123.
[67] H. Li, X. Fu, L. Zhang, Q. Huang, Z. Wu, T. Sun, Research of PDGF-BB gel on the wound healing of diabetic rats and its pharmacodynamics, J. Surg. Res. 145 (2008) 41–48.
[68] R. Lobmann, C. Zemlin, M. Motzkau, K. Reshke, H. Lehnert, Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing, J. Diabetes Complicat. 20 (2006) 329–335.
[69] R. Tsuboi, D.B. Rifkin, Recombinant basic fibroblast growth factor stimulates wound healing in healing-impaired db/db mice, Int. J. Clin. Exp. Med. Res. 172 (1990) 245–251.
[70] L.G. Presta, H. Chen, S.J. O'Connor, V. Chisholm, Y.G. Meng, et al., Humanization

of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders, Cancer Res. 57 (1997) 4593–4599.
[71] L.S. Angelo, R. Kurzrock, Vascular endothelial growth factor and its relationship to inflammatory mediators, Clin. Cancer Res. 13 (2007) 2825–2830.
[72] K. Zhou, Y. Ma, M.S. Brogan, Chronic and non-healing wounds: the story of vascular endothelial growth factor, Med. Hypotheses 85 (2015) 399–404.
[73] J.T. Hardwicke, J. Hart, A. Bell, R. Duncan, D.W. Thomas, R. Moseley, The effect of dextrin-rhEGF on the healing of full-thickness, excisional wounds in the (db/db) diabetic mouse, J. Control. Release 152 (2011) 411–417.
[74] D.L. Brown, C.D. Kane, S.D. Chernausek, et al., Differential expression and localization of insulin-like growth factors I and II in cutaneous wounds of diabetic and non-diabetic mice, Am. J. Pathol. 151 (1997) 715–724.
[75] B. Bruhn-Olszewska, A. Korzon-Burakowska, M. Gabig-Ciminska, et al., Molecular factors involved in the development of diabetic foot syndrome, Acta Biochim. Pol. 59 (2012) 507–513.
[76] F.Y. Bhora, B.J. Dunkin, S. Batzri, H.M. Aly, B.L. Bass, A.N. Sidawy, et al., Effect of growth factors on cell proliferation and epithelialization in human skin, J. Surg. Res. 59 (1995) 236–244.
[77] A.B. Roberts, Transforming growth factor-β: activity and efficacy in animal models of wound healing, Wound Repair Regen. 3 (1995) 408–418.
[78] O. Stojadinovic, I. Pastar, K.A. Gordon, M. Tomic-Canic, Physiology and pathophysiology of wound healing in diabetes, in: A. Veves, J.M. Giurini, F.W. LoGerfo (Eds.), The Diabetic Foot. Humana Press Inc, New York, 2000, pp. 127–149.
[79] W.N. Hozzein, G. Badr, A.A. Al Ghamdi, A. Sayed, N.S. Al-Waili, O. Garraud, 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 (2015) 940–954.
[80] E.B. Jude, Transforming growth factor-beta 1, 2, 3 and receptor type I and II in diabetic foot ulcers, Diabetes Med. 19 (2002) 440–447.
[81] H. Heublein, A. Bader, S. Giri, Preclinical and clinical evidence for stem cell therapies as treatment for diabetic wounds, Drug Discov. Today 20 (2015) 6.
[82] D.G. Armstrong, E.B. Jude, The role of matrix metalloproteinases in wound healing, J. Am. Podiatr. Med. Assoc. 92 (2002) 12–18.
[83] R. Lobmann, T.T. Pap, A. Ambrosch, K. Waldmann, W. Kfnig, H. Lehnert, Differential effects of PDGF-BB on matrix metalloproteases and cytokine release in fibroblasts of Type 2 diabetic patients and normal controls in vitro, J. Diabetes Comp. 20 (2006) 105–112.
[84] S.V. McLennan, D. Min, D.K. Yue, Matrix metalloproteinases and their roles in poor wound healing in diabetes, Wound Pract. Res. 16 (2008) 116–121.
[85] S.J. Wall, D. Bevan, D.W. Thomas, G. Keith, K.G. Harding, et al., Differential expression of matrix metalloproteinase during impaired wound healing of the diabetes mouse, J. Invest. Dermatol. 119 (91-) (2002) 98.
[86] R.G. Sibbald, K.Y. Woo, The biology of chronic foot ulcers in persons with DM, Diabetes/Metabolism Research & Review 24 (2008) S25–S30.
[87] J.P. Tardivo, F. Adami, J.A. Correa, M.A.S. Pinhal, M.S. Baptista, A clinical trial testing the efficacy of PDT in preventing amputation in diabetic patients, Photodiagnosis Photodyn. Ther. 11 (3) (2014) 342–350.
[88] M.R. Asadi, G. Torkaman, M. Hedayati, M.R. Mohajeri-Tehrani, M. Ahmadi, R.F. Gohardani, Angiogenic effects of low-intensity cathodal direct current on ischemic diabetic foot ulcers: a randomized controlled trial, Diabetes Res. Clin. Pract. 127 (2017) 147–155.
[89] Z. Soleimani, F. Hashemdokht, F. Bahmani, M. Taghizadeh, M. Memarzadeh, Z. Asem, Clinical and metabolic response to flaxseed oil omega-3 fatty acids supplementation in patients with diabetic foot ulcer: a randomized, doubleblind, placebo-controlled trial, J. Diabetes Complicat. 31 (9) (2017) 1394–1400.
[90] Y. Yang, T. Xia, W. Zhi, L. Wei, J. Weng, C. Zhang, et al., Promotion of skin regeneration in diabetic rats by electrospun core-sheath fibers loaded with basic fibroblast growth factor, Biomaterials 32 (2011) 4243–4254.
[91] M.W. Tsang, W.K.R. Wong, C.S. Hung, K.M. Lai, W. Tang, et al., Human epidermal growth factor enhances healing of diabetic foot ulcers, Diabetes Care 26 (2003) 1856–1862.
[92] X. Dong, J. Xu, W. Wang, H. Luo, X. Liang, L. Zhang, et al., Repair effect of diabetic ulcers with recombinant human epidermal growth factor loaded by sustained-release microspheres, Sci. China Life Sci. 51 (2008) 1039–1044.
[93] N. Morimoto, K. Yoshimura, M. Niimi, T. Ito, H. Tada, S. Teramukai, et al., An exploratory clinical trial for combination wound therapy with a novel medical matrix and fibroblast growth factor in patients with chronic skin ulcers: a study protocol, Am. J. Transl. Res. 4 (2012) 52–59.
[94] B. Cheng, H.W. Liu, X.B. Fu, T.Z. Sun, Z.Y. Sheng, Recombinant human platelet-derived growth factor enhanced dermal wound healing by a pathway involving ERK and c-fos in diabetic rats, J. Dermatol. Sci. 45 (2007) 193–201.
[95] X. Yan, B. Chen, Y. Lin, Y. Li, Z. Xiao, et al., Acceleration of diabetic wound healing by collagen-binding vascular endothelial growth factor in diabetic rat model, Diabetes Res. Clin. Pract. 90 (2010) 66–72.
[96] W. Wang, S. Lin, Y. Xiao, Y. Huang, Y. Tan, L. Cai, X. Li, Acceleration of diabetic wound healing with chitosan crosslinked collagen sponge containing recombinant human acidic fibroblast growth factor in healing-impaired STZ diabetic rats, Life Sci. 82 (2008) 190–204.
[97] J.S. Choi, K.W. Leong, H.S. Yoo, In vivo wound healing of diabetic ulcers using electrospun nanofibers immobilized with human epidermal growth factor (EGF), Biomaterials 29 (2008) 587–596.
[98] Y. Matsumoto, Y. Kuroyanagi, Development of a wound dressing composed of hyaluronic acid sponge containing arginine and epidermal growth factor, J. Biomater. Sci. Polym. Ed. 21 (2010) 715–726.
[99] N. Kanda, N. Morimoto, A.A. Ayvazyan, S. Takemoto, K. Kawai, Y. Nakamura, et al., Evaluation of a novel collagen-gelatin scaffold for achieving the sustained release of basic fibroblast growth factor in a diabetic mouse model, J. Tissue Eng. Regen. Med. 8 (2014) 29–40.
[100] P. Koria, H. Yagi, Y. Kitagawa, Z. Megeed, Y. Nahmias, R. Sheridan, et al., Self-assembling elastin-like peptides growth factor chimeric nanoparticles for the treatment of chronic wounds, Proc. Natl. Acad. Sci. 108 (2011) 1034–1039.
[101] Y. Yang, T. Xia, F. Chen, W. Wei, C. Liu, S. He, et al., Electrospunfibers with plasmid bFGFpolyplex loadings promote skin wound healing in diabetic rats, Mol. Pharm. 9 (2012) 48–58.
[102] Z. Xie, C.B. Paras, H. Weng, P. Punnakitikashem, L.C. Su, et al., Dual growth factor releasing multi-functional nanofibers for wound healing, Acta Biomater. 9 (2013) 9351–9359.
[103] R. Judith, M. Nithya, C. Rose, A.B. Mandal, Application of a PDGF- containing novel gel for cutaneous wound healing, Life Sci. 87 (2010) 1–8.
[104] R.K. Chan, P.H. Liu, G. Pietramaggiori, S.I. Ibrahim, H.B. Hechtman, D.P. Orgill, Effect of recombinant platelet-derived growth factor (Regranex) on wound closure in genetically diabetic mice, J. Burn. Care Res. 27 (2006) 202–205.
[105] K. Mizuno, K. Yamamura, K. Yano, T. Osada, S. Saeki, N. Takimoto, et al., Effect of chitosan film containing basic fibroblast growth factor on wound healing in genetically diabetic mice, J. Biomed. Mater. Res. 64 (2003) 177–181.
[106] D.G. Pyun, H.J. Choi, H.S. Yoon, T. Thambi, D.S. Lee, Polyurethane foam containing rhEGF as a dressing material for healing diabetic wounds: synthesis, characterization, in vitro and in vivo studies, Colloids Surf. B: Biointerface 135 (2015) 699–706.
[107] K.K. Chereddy, A. Lopes, S. Koussoroplis, V. Payen, C. Moia, et al., Combined effects of PLGA and vascular endothelial growth factor promote the healing of non-diabetic and diabetic wounds, Nanomedicine (2015) 1–11, https://doi.org/10.1016/j.nano.2015.07.006.
[108] T. Laing, R. Hanson, F. Chan, D. Bouchier-Hayes, Effect of pravastatin on experimental diabetic wound healing, J. Surg. Res. 161 (2010) 336–340.
[109] M. Bagheri, B.M. Jahromi, H. Mirkhani, Z. Solhjou, A. Noorafshan, et al., Azelnidipine, a new calcium channel blocker, promotes skin wound healing in diabetic rats, J. Surg. Res. 169 (2011) e101–e107.
[110] Y. Lee, J.J. Chang, M.C. Yang, C.T. Chien, W.F. Lai, Acceleration of wound healing in diabetic rats by layered hydrogel dressing, Carbohydr. Polym. 88 (2012) 809–819.
[111] U.F. Aly, Preparation and evaluation of novel topical gel preparations for wound healing in diabetics, Int. J. Pharm. Pharm. Sci. 4 (2012) 76–77.
[112] S. Hamed, Y. Ullmann, M. Masoud, E. Hellou, Z. Khamaysi, L. Teot, Topical erythropoietin promotes wound repair in diabetic rats, J. Invest. Dermatol. 130 (2010) 87–94.
[113] S. Babaei, N. Bayat, M. Nouruzian, M. Bayat, Pentoxifylline improves cutaneous wound healing in streptozotocin-induced diabetic rats, Eur. J. Pharmacol. 700 (2013) 165–172.
[114] Z. Hou, C. Nie, Z. Si, Y. Ma, Deferoxamine enhances neovascularization and accelerates wound healing in diabetic rats via the accumulation of hypoxia-inducible factor-1α, Diabetes Res. Clin. Pract. (2013) 62–71.
[115] M. Ram, V. Singh, S. Kumawat, D. Kumar, M.C. Lingaraju, et al., Deferoxamine modulates cytokines and growth factors to accelerate cutaneous wound healing in diabetic rats, Eur. J. Pharmacol. 764 (2015) 9–21.
[116] J.R. Scott, R.N. Tamura, P. Muangman, F.F. Isik, C. Xie, N.S. Gibran, Topical substance P increases inflammatory cell density in genetically diabetic murine wounds, Wound Repair Regen. 16 (2008) 529–533.
[117] V. Kant, A. Gopal, D. Kumar, N.N. Pathak, et al., Curcumin-induced angiogenesis hastens wound healing in diabetic rats, J. Surg. Res. 193 (2015) 978–988.
[118] E.C. Leal, E. Carvalho, A. Tellechea, A. Kafanas, F. Tecilazich, C. Kearney, et al., Substance P promotes wound healing in diabetes by modulating inflammation and macrophage phenotype, Am. J. Pathol. 185 (2015) 1638–1648.
[119] B. Romana-Souza, A.P. Nascimento, A. Monte-Alto-Costa, Propranolol improves cutaneous wound healing in streptozotocin-induced diabetic rats, Eur. J. Pharmacol. 6 (11) (2009) 77–84.
[120] C.H. Lee, S.H. Chang, W.J. Chen, K.C. Hung, S.J. Liu, et al., Augmentation of diabetic wound healing and enhancement of collagen content using nano-fibrous glucophage-loaded collagen/PLGA scaffold membranes, J. Colloid Interface Sci. 439 (2015) 88–97.
[121] P. Kaur, A.K. Sharma, D. Nag, A. Das, S. Datta, A. Ganguli, V. Goel, S. Rajput, G. Chakrabarti, B. Basu, D. Choudhury, Novel nano-insulin formulation modulates cytokine secretion and remodeling to accelerate diabetic wound healing, Nanomedicine (2018), https://doi.org/10.1016/j.nano.2018.08.013.
[122] X. Wang, M.K. Sng, S. Foo, H.C. Chong, M.B.Y. Tang, et al., Early controlled release of peroxisome proliferator-activated receptor β/δ agonist GW501516 improves diabetic wound healing through redox modulation of wound microenvironment, J. Control. Release 197 (2015) 138–147.
[123] A.J. Whittam, Z.N. Maan, D. Duscher, J.A. Barrera, M.S. Hu, L.H. Fischer, et al., Small molecule inhibition of dipeptidyl Peptidase-4 enhances bone marrow progenitor cell function and angiogenesis in diabetic wounds, Transl. Res. (2018), https://doi.org/10.1016/j.trsl.2018.10.006.
[124] F. Lv, J. Wang, P. Xu, Y. Han, H. Ma, H. Xu, S. Chen, J. Chang, Q. Ke, M. Liu, Z. Yi, C. Wu, A conducive bioceramic/polymer composite biomaterial for diabetic wound healing, Acta Biomater. (2017), https://doi.org/10.1016/j.actbio.2017.07.020.
[125] J.G. Leu, M.H. Chiang, C.Y. Chen, J.T. Lin, H.M. Chen, Y.L. Chen, Y.L. Liang, Adenine accelerated the diabetic wound healing by PPAR delta and angiogenic regulation, Eur. J. Pharmacol. (2017), https://doi.org/10.1016/j.ejphar.2017.11.027.
[126] N.H. Wael, G. Badr, B.M. Badre, A. Allam, et al., Bee venom improves diabetic wound healing by protecting functional macrophages from apoptosis and

enhancing Nrf2, Ang-1 and Tie-2 signaling, Mol. Immunol. 103 (2018) 322–335.
[127] U. Bulbake, S. Jain, N. Kumar, A. Mittal, Curcumin loaded biomimetic composite graft for faster regeneration of skin in diabetic wounds, J. Drug Deliv. Sci. Technol. (2018), https://doi.org/10.1016/j.jddst.2018.06.016.
[128] T. Kawanabe, T. Kawakami, Y. Yatomi, S. Shimada, Y. Soma, Sphingosine 1-phosphate accelerates wound healing in diabetic mice, J. Cosmet. Dermatol. Sci. Appl. 48 (2007) 53–60.
[129] K. Kawai, A. Kageyama, T. Tsumano, S. Nishimoto, K. Fukuda, et al., Effects of adiponectin on growth and differentiation of human keratinocytes-Implication of impaired wound healing in diabetes, Biochem. Biophys. Res. Commun. 374 (2008) 269–273.
[130] L.I.F. Moura, A.M.A. Dias, E.C. Leal, L. Carvalho, H.C. De Sousa, E. Carvalho, Chitosan-based dressings loaded with Neurotensin—an efficient strategy to improve early diabetic wound healing, Acta Biomater. 2 (2014) 843–857.
[131] L.I.F. Moura, A.M.A. Dias, E. Suesca, S. Casadiegos, E.C. Leal, et al., Neurotensin-loaded collagen dressings reduce inflammation and improve wound healing in diabetic mice, Biochim. Biophys. Acta 1842 (2014) 32–43.
[132] M. Galeano, F. Polito, A. Bitto, N. Irrera, G.M. Campo, et al., Systemic administration of high-molecular weight hyaluronan stimulates wound healing in genetically diabetic mice, Biochim. Biophys. Acta 1812 (2011) 752–759.
[133] S.L. Hansen, C.A. Myers, A. Charboneau, D.M. Young, N. Boudreau, HoxD3 accelerates wound healing in diabetic mice, Am. J. Pathol. 163 (2003) 2421–2431.
[134] A. Bazrafshan, M. Owji, M. Yazdani, M. Varedi, Activation of mitosis and angiogenesis in diabetes-impaired wound healing by processed human amniotic fluid, J. Surg. Res. 188 (2014) 545–552.
[135] M.K. Maharlooei, M. Bagheri, Z. Solhjou, B.M. Jahromi, M. Akrami, et al., Adipose tissue derived mesenchymal stem cell (AD-MSC) promotes skin wound healing in diabetic rats, Diabetes Res. Clin. Pract. 93 (2001) 228–234.
[136] P. Velander, C. Theopold, O. Bleiziffer, et al., Cell suspensions of autologous keratinocytes or autologous fibroblasts accelerate the healing of full thickness skin wounds in a diabetic porcine wound healing model, J. Surg. Res. 157 (2009) 14–20.
[137] S. Kazemi-Darabadi, F. Sarrafzadeh-Rezaei, A.A. Farshid, B. Dalir-Naghadeh, Allogenous skin fibroblast transplantation enhances excisional wound healing following alloxan diabetes in sheep, a randomized controlled trial, Int. J. Surg. 12 (2014) 751–756.
[138] V. Falanga, S. Iwamoto, M. Chartier, T. Yufit, J. Butmarc, N. Kouttab, et al., Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds, Tissue Eng. 13 (2007) 1299–1312.
[139] Y.R. Kuo, C.T. Wang, J.T. Cheng, et al., Bone marrow-derived mesenchymal stem cells enhanced diabetic wound healing through recruitment of tissue regeneration in a rat model of streptozotocin-induced diabetes, Plast. Reconstr. Surg. 128 (2011) 872–880.
[140] C. Gu, S. Huang, D. Gao, Y. Wu, J. Li, et al., Angiogenic effect of mesenchymal stem cells as a therapeutic target for enhancing diabetic wound healing, Int. J. Lower Extrem. Wounds 13 (2014) 88–93.
[141] T.G. Nithya, Efficacy of mesenchymal stem cell incorporation in different composite electrospun collagen nanofibers for diabetic wound healing, Asian J. Pharm. Clin. Res. 6 (2013) 149–152.
[142] K.B. Lee, J. Choi, S.B. Cho, J.Y. Chung, E.S. Moon, et al., Topical embryonic stem cells enhance wound healing in diabetic rats, J. Orthop. Res. 29 (2011) 1554–1562.
[143] S.W. Kim, H.Z. Zhang, L. Guo, J.M. Kim, M.H. Kim, Amniotic mesenchymal stem cells enhance wound healing in diabetic NOD/SCID mice through high angiogenic and engraftment capabilities, PLoS One 7 (2012) e41105.
[144] P. Kong, X. Xie, F. Li, Y. Liu, Y. Lu, Placenta mesenchymal stem cell accelerates wound healing by enhancing angiogenesis in diabetic Goto-Kakizaki (GK) rats, Biochem. Biophys. Res. Commun. 438 (2013) 410–419.
[145] E.H. Javazon, S.G. Keswani, A.T. Badillo, T.M. Crombleholme, et al., Enhanced epithelial gap closure and increased angiogenesis in wounds of diabetic mice treated with adult murine bone marrow stromal progenitor cells, Wound Repair Regen. 15 (2007) 350–359.
[146] M. Nambu, S. Kishimoto, S. Nakamura, H. Mizuno, S. Yanagibayashi, et al., Accelerated wound healing in healing-impaired db/db mice by autologous adipose tissue-derived stromal cells combined with atelocollagen matrix, Ann. Plast. Surg. 62 (2009) 317–321.
[147] D. Ma, J.E.H. Kua, W.K. Lim, S.T. Lee, A.W.C. Chua, In vitro characterization of human hair follicle dermal sheath mesenchymal stromal cells and their potential in enhancing diabetic wound healing, Cytotherapy 17 (2015) 1036–1051.
[148] D.C.S. Pedroso, A. Tellechea, L. Moura, I. Fidalgo-Carvalh, J. Duarte, et al., Improved survival, vascular differentiation and wound healing potential of stem cells Co-cultured with endothelial cells, PLoS One 6 (2011) e16114.
[149] Q. Xu, A. Sigen, Y. Gao, L. Guo, J. Creagh-Flynn, D. Zhou, U. Greiser, Y. Dong, F. Wang, H. Tai, W. Liu, W. Wang, W. Wang, A hybrid injectable hydrogel from hyperbranched PEG macromer as a stem cell delivery and retention platform for diabetic wound healing, Acta Biomater. (2018), https://doi.org/10.1016/j.actbio.2018.05.039.
[150] R.F. Irons, K.W. Cahill, D.A. Rattigan, J.H. Marcotte, M.W. Fromer, S. Shaohua Chang, et al., Acceleration of diabetic wound healing with adipose-derived stem cells, endothelial-differentiated stem cells, and topical conditioned medium therapy in a swine model, J. Vasc. Surg. (2018), https://doi.org/10.1016/j.jvs.2018.01.065.
[151] K.C. Moon, J.S. Lee, S.K. Han, H.W. Lee, E.S. Dhong, Effects of human umbilical cord blood–derived mesenchymal stromal cells and dermal fibroblasts on diabetic wound healing, Cytotherapy (2017), https://doi.org/10.1016/j.jcyt.2017.03.074.
[152] M.A. Abu-Al-Basal, Healing potential of Rosmarinus officinalis L. On full-thickness excision cutaneous wounds in alloxan-induced-diabetic BALB/c mice, J. Ethnopharmacol. 131 (2010) 443–450.
[153] A. Singha, S. Bajpaia, N. Singha, V. Kumara, J.K. Goura, et al., Wound healing activity of standardized extract of Curculigo orchioides in streptozotocin–induced diabetic mice, Asian Pac. J. Trop. Dis. 4 (2014) S48–S53.
[154] B. Larijani, R. Heshmat, A. Bahrami, H. Delshad, et al., Effect of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: a multicenter clinical trial, Daru J. Pharm. Sci. 16 (2008) 35–40.
[155] T.W. Lau, F.F.Y. Lam, K.M. Lau, Y.W. Chan, K.M. Lee, et al., Pharmacological investigation on the wound healing effects of Radix rehmanniae in an animal model of diabetic foot ulcer, J. Ethnopharmacol. 123 (2009) 155–162.
[156] J.G. Merrel, S.W. McLaughlin, L. Tie, C.T. Laurencin, A.F. Chen, L.S. Nair, Curcumin loaded poly(e-caprolactone) nanofibres: diabetic wound dressing with anti-oxidant and anti-inflammatory properties, Clin. Exp. Pharmacol. Physiol. Suppl. 36 (2009) 1149–1156.
[157] V. Kant, A. Gopal, N.N. Pathak, P. Kumar, et al., Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats, Int. Immunopharmacol. 20 (2014) 322–330.
[158] V. Kant, D. Kumar, D. Kumar, R. Prasad, A. Gopal, P. Kumar, et al., Topical application of substance P promotes wound healing in streptozotocin-induced diabetic rats, Cytokine 73 (2015) 144–155.
[159] S. Lodhi, A.K. Singhai, Wound healing effect of flavonoid rich fraction and luteolin isolated from *Martynia annua* Linn. On streptozotocin induced diabetic rats, Asian Pac. J. Trop. Med. (2013) 253–259.
[160] L. Tie, Y. An, J. Han, Y. Xiao, Y. Xiaokaiti, S. Fan, S. Liu, A.F. Chen, X. Li, Genistein accelerates refractory wound healing by suppressing superoxide and FoxO1/iNOS pathway in type 1 diabetes, J. Nutr. Biochem. 24 (2013) 88–96.
[161] N. Fujita, I. Sakaguchi, H. Kobayashi, N. Ikeda, Y. Kato, et al., An extract of the root of Lithospermunerythrorhison accelerates wound healing in diabetic mice, Biol. Pharm. Bull. 26 (2003) 329–335.
[162] J.C.W. Tam, C.H. Ko, K.M. Lau, M.H. To, H.F. Kwok, et al., A Chinese 2-herb formula (NF3) promotes hindlimb ischemia-induced neovascularization and wound healing of diabetic rats, J. Diabetes Complicat. 28 (2014) 436–447.
[163] J.C.W. Tam, K.M. Lau, C.L. Liu, M.H. To, H.F. Kwok, et al., The in vivo and in vitro diabetic wound healing effects of a 2-herb formula and its mechanisms of action, J. Ethnopharmacol. 134 (2011) 831–838.
[164] T. Ponrasu, L. Suguna, Efficacy of Annona squamosa on wound healing in streptozotocin-induced diabetic rats, Int. Wound J. 9 (2012) 613–623.
[165] J. Jacobi, J.J. Jang, U. Sundram, H. Dayoub, L.F. Fajardo, J.P. Cooke, Nicotine accelerates angiogenesis and wound healing in genetically diabetic mice, Am. J. Pathol. 161 (2002) 97–104.
[166] M. Zuber, V. Rajesh, K. Anusha, C.R. Reddy, A. Tirupathi, Wound healing activity of ethanolic extract of Allium sativum on alloxan induced diabetic rats, Int. J. Sci. Invent. Today 2 (2013) 40–57.
[167] A.D. Kandhare, P. Ghosh, S.L. Bodhankar, Naringin, a flavanone glycoside, promotes angiogenesis and inhibits endothelial apoptosis through modulation of inflammatory and growth factor expression in diabetic foot ulcer in rats, Chem.-Biol. Interact. 219 (2014) 101–112.
[168] P. Inpanya, A. Faikrua, A. Ounaroon, A. Sittichokechaiwut, J. Viyoch, Effects of the blended fibroin/aloe gel film on wound healing in streptozotocin-induced diabetic rats, Biomed. Mater. 7 (2012) 035008.
[169] A.H. Kwon, Z. Qiu, M. Hashimoto, K. Yamamoto, T. Kimura, Effects of medicinal mushroom (Sparassis crispa) on wound healing in streptozotocin-induced diabetic rats, Am. J. Surg. 197 (2009) 503–509.
[170] P. Molan, Honey Based Wound Dressings, USRE42755 E (2011).
[171] H. Mohamed, B.E.I. Lenjawi, M.A. Salma, S. Abdi, Honey based therapy for the management of a recalcitrant diabetic foot ulcer, J. Tissue Viability 23 (2014) 29–33.
[172] Y. Yang, F. Wang, D. Yin, Z. Fang, L. Huang, Astragulus polysaccharide-loaded fibrous mats promote the restoration of microcirculation in/around skin wounds to accelerate wound healing in a diabetic rat model, Colloid Surf. B Biointerfaces (2015), https://doi.org/10.1016/j.colsurfb.2015.09.006.
[173] X. Zhang, Z. Ma, Y. Wang, Y. Li, B. Sun, X. Guo, C. Pan, L. Chen, The four-herb chinese medicine formula Tuo-Li-Xiao-Du-San accelerates cutaneous wound healing in streptozotocin-induced diabetic rats through reducing inflammation and increasing angiogenesis, J. Diabetes Res. 5 (2016) 639129, 11.
[174] R.R. Ahmed, A. Mahmoud, O.M. Ahmed, A. Metwalli, H. Ebaid, Up-regulation of Hsp72 and keratin16 mediates wound healing in streptozotocin diabetic rats, Biol. Res. 48 (2015) 54–66.
[175] G. Badr, B.M. Badr, M.H. Mahmoud, M. Mohany, D.M. Rabah, O. Garraud, Treatment of diabetic mice with undenatured whey protein accelerates the wound healing process by enhancing the expression of MIP-1α, MIP-2, KC, CX3CL1 and TGF-β in wounded tissue, BMC Immunol. 13 (2012) 32–41.
[176] J.P. Barret, F. Podmelle, B. Lipový, H.O. Rennekampff, H. Schumann, A. Schwieger-Briel, et al., Accelerated re-epithelialization of partial-thickness skin wounds by a topical betulin gel: results of a randomized phase III clinical trials program, Burns 4 (2017) 1284–1294.
[177] C.L. Guo, X.Y. Fu, Research on effect evaluation of local treatment of patients with diabetic foot ulcers using honey dressing, Med. J. West China 7 (2013) 977–980.
[178] M. Siavash, S. Shokri, S. Haghighi, M.A. Shahtalebi, Z. Farajzadehgan, The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial, Int. Wound J. 12 (2015) 137–142.
[179] A.V. Kamaratos, K.N. Tzirogiannis, S.A. Iraklianou, G.I. Panoutsopoulos, I.E. Kanellos, A.I. Melidonis, Manuka honey-impregnated dressings in the treatment of neuropathic diabetic foot ulcers, Int. Wound J. 11 (2014) 259–263.

[180] F. Namjoyan, F. Kiashi, Z.B. Moosavi, F. Saffari, B.S. Makhmalzadeh, Efficacy of Dragon's blood cream onwound healing: a randomized, double-blind, placebo controlled clinical trial, J. Tradit. Complement. Med. (2015) 1–4.

[181] M.T.A. Omar, A. Alghadir, K.K. Al-Wahhabi, A.B. Al-Askar, Efficacy of shock wave therapy on chronic diabetic foot ulcer: a single-blinded randomized controlled clinical trial, Diabetes Res. Clin. Pract. (2014), https://doi.org/10.1016/j.diabres.2014.09.024.

[182] M.H. Mohammadi, B. Molavi, S. Mohammadi, M. Nikbakht, A.M. Mohammadi, S. Mostafaei, A.H. Norooznezhad, A.G. Abdegah, A. Ghavamzadeh, Evaluation of wound healing in diabetic foot ulcer using platelet-rich plasma gel: a single-arm clinical trial, Transfus. Apher. Sci. (2016), https://doi.org/10.1016/j.transci.2016.10.020.

[183] F. Game, W. Jeffcoate, L. Tarnow, J.L. Jacobsen, D.J. Whitham, E.F. Harrison, S.J. Ellender, D. Fitzsimmons, M. Löndahl, LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial, Lancet Diabetes Endocrinol. S2213-8587 (18) (2018) 30240–30247, https://doi.org/10.1016/.

[184] G. Sepulveda, M. Espindola, M. Maureira, E. Sepúlveda, J.I. Fernández, C. Oliva, A. Sanhueza, M. Vial, C. Manterola, Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation: a randomised controlled trial, Cir. Esp. 86 (3) (2009) 171–177.