Leveraging Potential of Nanotherapeutics in Management of Diabetic Foot Ulcer

Authors
Supriya Pandey, Mohammad Shaif, Tarique M Ansari, Arshiya Shamim, Poonam Kushwaha

Affiliation
Faculty of Pharmacy, Integral University, Dasauli-Kursi Road, Lucknow, India

Key words
Nanotechnology, diabetes mellitus, diabetic foot ulcer, wound healing, pathophysiology, nanotherapeutics

received 14.10.2021
revised 10.01.2022
accepted 18.01.2022
published online 03.03.2022

Bibliography
Exp Clin Endocrinol Diabetes 2022; 130: 678–686
DOI 10.1055/a-1749-4909
ISSN 0947-7349

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Poonam Kushwaha
Faculty of Pharmacy
Integral University
Lucknow
India
poonam.kushwaha083@gmail.com

ABSTRACT

Diabetic foot ulcers (DFUs) are the most common complications associated with diabetes mellitus. DFUs are displayed as open sores or wounds located on the bottom of the foot as a secondary complication of diabetes mellitus (DM). DFUs are associated with significant morbidity and mortality and can subsequently lead to hospitalization and lower limb amputation if not recognized and treated on time. An immense challenge to conventional treatments is caused by the chronic nature of diabetic foot syndrome and it has led to the emergence of nanotechnology-based therapeutics. The greatest advantages of these nanotherapeutics are their unique biological, chemical, and physical properties. The present review highlights the augmentation of bacterial infections relating to delayed healing of DFUs and the potential of nanotherapeutics such as polymeric nanoparticles, metallic nanoparticles, siRNA-based nanoparticles, lipid nanoparticles, and nanofibers in accelerating wound healing in diabetic foot ulcers.

Introduction

A diabetic foot ulcer (DFU) is an open sore or wound that most likely occurs at the bottom of the foot or toes where repetitive trauma and pressure are encountered. It is the major complication of uncontrolled diabetes mellitus associated with a high degree of morbidity and mortality [1]. DFU can be caused by inadequate glycemic control, peripheral vascular disease, or poor foot care and is also one of the most common causes of osteomyelitis and amputations of the lower extremities [2]. The occurrence of DFU can be identified by several common symptoms and signs, including drainage on the person's socks, redness, and swelling. Occasionally, an odor may occur if the ulcer has progressed significantly [3].

The battling issues faced by these ulcers are impaired or delayed wound healing. Wound healing is an innate mechanism of action that works reliably most of the time. During the healing process, damaged wound tissue is restored to its original state by a series of biomolecular and cellular processes. Cell migration/proliferation, inflammation, and remodeling are the fundamental biological processes involved in wound healing [4]. In wound healing, stepwise repair of the extracellular matrix (ECM) is vital to the overall healing process. These diseases can cause impairment of biochemical signaling, ECM deposition, and cell migration, which can ultimately lead to DFU progression [3].

DFUs have a multifactorial etiology. Low blood sugar levels, calluses, foot deformities, excessively tight footwear, underlying peripheral neuropathy, poor circulation, dry skin, etc. are all potential contributing factors. About 60 % of diabetics develop neuropathy, which eventually results in foot ulcers. In people with a flat foot, the risk of developing a foot ulcer increases since they have dispro-

portionate stress across the foot, resulting in tissue inflammation in high-risk areas [5].

Global Epidemiology of DFU

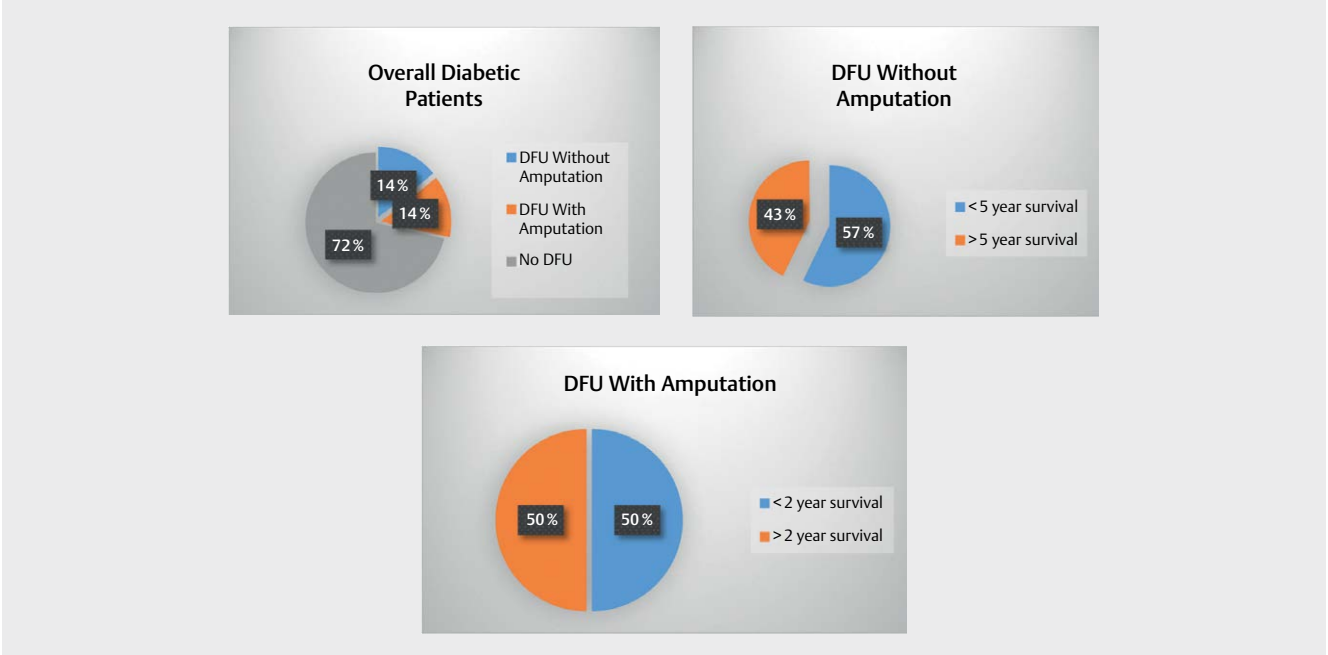
DFU has become a major global epidemic and has shown an increasing trend over previous years. The annual incidence of DFUs worldwide is between 9.1 to 26.1 million. Around 15 to 25 % of patients with diabetes mellitus (DM) will develop a DFU during their lifetime [2]. As the number of newly diagnosed diabetics is increasing yearly, the incidence of a DFU is also bound to increase. DFUs can occur at any age but are most prevalent in patients with diabetes mellitus ages 45 and over [3]. Approximately 405.6 million adults worldwide are affected with type 2 diabetes and are predicted to reach more than 510.8 million by 2030 [1]. Overall, the rate of lower limb amputation in patients with DM is 15 times higher than in patients without diabetes [4]. About 19–34 % of patients with diabetes are expected to be affected with DFUs while the occurrence of DFUs is expected to be more frequent in aged patients [5]. Approximately 405.6 million adults are affected with type 2 diabetes around the world and are predicted to reach more than 510.8 million by 2030 [6]. About 15–25 % of diabetic patients can develop foot ulcers which eventually lead to amputation [7]. Epidemiological studies show that the number of patients with DM increased from about 30 million cases in 1985, 177 million in 2000, 285 million in 2010, and is estimated that with the current rate, more than 360 million people by 2030 will have DM [8, 9]. In total it is estimated that 15 % of patients with diabetes will suffer from DFU during their lifetime. While it is difficult to obtain accurate figures for the prevalence of DFU, still the prevalence of this complication ranges from 4–27 %. Early effective management of DFU can reduce the severity of complications such as preventable amputations and possible mortality, and also can improve the overall quality of life as per the strategies of the National Institute for Health and Clinical Excellence [10]. ▶ **Fig. 1** illustrates the DFUs incidence in the diabetic population and respective overall life expectancies according to DFU treatment (amputation vs. no amputation).

Pathophysiology of DFU

DFUs are one of the most frequent complications of diabetes, resulting from a complex interaction of factors, namely ischemia, and neuropathy. Neuropathy, which is characterized by modifications insensitive and autonomic functions, causes ulceration due to trauma or excessive pressure in a deformed foot without protective sensibility [3]. Autonomic neuropathy causes dryness of the skin by decreasing the sweating, and therefore increasing the vulnerability of the skin to break down. Once the protective layer of skin is damaged, deep tissues are exposed to bacterial colonization [11]. Diabetes-associated ischemia is caused by peripheral arterial disease. Poor arterial inflow decreases blood supply to the ulcer area and is associated with reduced oxygenation, nutrition, and ulcer healing [4]. These ulcers are frequently colonized by pathogenic bacteria and infection is facilitated by immunological deficits related to diabetes, rapidly progressing to deeper tissues, increasing the presence of necrotic tissue, rendering amputation inevitable [2]. Diabetic patients frequently require minor or major amputations of the lower limbs (15–27 %), which not only contribute dramatically to high morbidity among diabetic patients but is also associated with severe clinical depression and increased mortality rates [12].

Risk factors

The major risk factors concerned in the development of DFUs include loss of protective sensation due to diabetic peripheral neu-



▶ **Fig. 1** Incidence of diabetic foot ulcers (DFUs) in diabetic population and respective overall life expectancies according to DFU treatment (amputation vs. no amputation) [9, 10].

ropathy where feet become numb and injury goes unnoticed and peripheral artery disease (PAD) which is associated with the development of DFUs [13]. Foot deformity and calluses can result in high plantar pressure, which may result in additional risk [11]. While other risk factors such as older aging, infections, poor glycemic control, diabetic neuropathy, cigarette smoking habit, peripheral vascular diseases, ischemia, previous foot ulceration, amputation, and reduced personal care have also been demonstrated to play roles in the pathogenesis and progression of diabetic foot ulceration [14]. DFUs may follow bacterial invasion resulting in infection and decay, in any part of the body especially in the distal part of the lower leg, and lead to lower limb amputation.

Biofilm and antimicrobial resistance in DFU

Biofilm formation is an important pathophysiological stage in DFU. It has a primary role in the disease progression and chronicity of the lesion, the development of antibiotic resistance, making it difficult to treat the wound [15]. Biofilms, by definition, are the ubiquitous and natural phenotype of bacteria. They typically consist of polymicrobial populations of cells, which are attached to a surface and encase themselves in hydrated extracellular polymeric substances. The main problem in DFU is the difficulty in distinguishing between infection and colonization [16]. The bacteria present in DFU are organized into functionally equivalent pathogroups that allow for close interactions between the bacteria within the biofilm. Consequently, some bacterial species that alone would be considered non-pathogenic, or incapable of maintaining a chronic infection, could co-aggregate symbiotically in a pathogenic biofilm and act synergistically to cause a chronic infection [17, 18]. Wound infection, faulty wound healing, and ischemia are the most common precursors to diabetes-related amputations. Indeed, 80 % of lower-limb amputations in diabetic patients are preceded by biofilm-infected foot ulceration. Infected wounds result in an increased risk of death within 18 months [19]. The host-microorganism interface plays a major role in DFU development. In DFU, bacteria are classically organized into functionally equivalent pathogroups, where pathogenic and commensal bacteria co-aggregate symbiotically in a pathogenic biofilm to maintain a chronic infection [20]. This polymicrobial biofilm has been observed both in pre-clinical studies using animal models and in clinical research on DFU. It represents the main cause of delayed healing. Bacteria that reside within mature biofilms are highly resistant to many traditional therapies. Currently, one of the most successful strategies for the management of biofilm-related conditions is the physical removal of the biofilm, such as frequent debridement of DFUs [21].

Management of Diabetic Foot Ulcers

All individuals with diabetes can develop foot ulcers, which can be prevented by good foot care. Treatment for DFUs varies depending on their causes. Therefore, the management of DFU is multidisciplinary and involves the regulation of blood glucose, treatment of infection, pressure off-loading, the use of wound dressing and topical agents, debridement, and the optimization of the vascular perfusion and oxygenation of the lower limb. However, despite optimal wound care, at least 30 % of the ulcers fail to heal within 20 weeks of treatment. The conventional methods have several limitations. One of the major limitations is the rate and progression of healing of a diabetic wound when adopting a conventional diabetic wound management therapy [13, 14].

As the treatment of DFU remains a challenge, novel therapies have been developed that can be used as an adjunct to conventional therapy. Several advanced standard procedures including the topical and systemic pharmacotherapies such as ischaemic ulcers, and a multi-layered patch of autologous leucocytes, platelets, and fibrin in ulcers with or without ischemia, placentally derived products, and topical and systemic oxygen therapy play a significant role in the healing of DFUs [21, 23]. Growth factors, bio-engineered tissues, stem cell therapy, gene therapy, and peptide therapy also have been suggested for the treatment of DFUs [24]. In addition to providing standard care, skin grafts and tissue replacements can be used to reconstruct skin defects for people with DFUs [25].

Nanotherapeutic Modalities in the Management of Diabetic Foot Ulcers

Mild and acute clinical cases can be managed with conventional or standard therapies alone but the chronic wounds and those appearing as secondary complications of metabolic disorders require intensive pharmaceutical care and pharmacotherapy [25]. The complications with chronic ulcerations and the failure of other conventional treatments paved the way for the emergence of nanotechnology-based therapeutic agents to tackle the complexity of diabetic wound healing [26]. In the past few years, several nanoformulations have emerged in the market that offer promising results for such patients. The development of nanotechnology has created a means of prolonging the bioavailability of target molecules at the wound site, intending to accelerate the healing process, avoide secondary complications, and improve patient compliance. Conceptually, the use of nanoformulations in cutaneous wound healing has major advantages [27].

Nanotechnology-based wound healing methods offer several advantages such as cell specificity, suitability for topical drug delivery, and sustainable and controlled release of encapsulated drugs for a required period until the wound heals. In the case of wound healing, nanoparticles are ideal for topical delivery, supporting better interactions with the biological target and increased penetration at the wound sites [24]. Nanoparticles have emerged as an emerging scientific and technological revolution in the management of DFUs. They have made major contributions to pharmaceutical applications and have been proved beneficial in the treatment of DFU [28, 29]. A combination of antibacterial nanoparticles like silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), copper nanoparticles (CuNPs), etc. with polymeric matrix could efficiently inhibit bacterial growth and at the same time speeds up the wound healing process. The present review aimed to discuss the most modern astonishing potential of polymeric nanoparticles, metallic nanoparticles, inorganic nanoparticles, lipid nanoparticles, siRNA-based nanoparticles, and nanofibrous structures in the management of DFU.

Studies on the use of nanotherapeutics for the treatment of diabetic foot ulcers: Preclinical status

Polymeric nanoparticles

Polymeric nanoparticles, specifically naturally occurring polymers like chitosan nanoparticles, have been studied for their antibacterial activity and pro-wound-healing properties. Polymeric nanomaterial therapy involves the use of polymeric materials as dressings or as delivery vehicles. There have been numerous conventional wound dressings that were employed for the management of DFUs; however, there is a lack of absolute and versatile choice, therefore polymer-based dressings are used for the treatment of DFUs. Due to the hydrophilic nature of polymers, they are generally employed in wound dressing or as drug-delivering systems. The wound healing properties of polymers are because of their moisture absorption capacity and water vapor transmission that allow the maintenance of the moist environment in the wound along with the collection of wound exudates. Both natural and synthetic polymers, as well as their combination, have been investigated for wound healing and antimicrobial mechanisms which may include Poly-lactic-co-glycolic acid (PLGA) nanoparticles, polycaprolactone (PCL), and polyethylene glycol (PEG). A very versatile range of naturally-originated polymers including chitosan (CS), hyaluronic acid (HA), cellulose, alginate, dextran, collagen, gelatin, elastin, fibrin, and silk fibroin which has been utilized for the treatment of DFUs [25, 26].

In the case of polymeric nanoparticles, chitosan, a natural polymer is used, due to its biocompatibility and antimicrobial activity. It is possible to encapsulate a wide range of natural components such as aloe vera, vitamin E, and curcumin, which have potentially beneficial effects on skin wound healing. PLGA, PCL, poly (lactic acid) (PLA), and PEG are synthetic polymers approved by the Food and Drug Administration (FDA). Among these polymers, PLGA is considered the most appropriate biodegradable polymer due to its ability to release lactate, a degradation byproduct. PLGA nanoparticles have been reported to stimulate cell proliferation and shorten the duration of wound healing in diabetic rats and despite moderate drug use, loading may be a promising delivery system for growth factors. Nanoparticles and biomolecules can be incorporated in hydrogels and thus, have opened the door to more advanced topical drug delivery with unique benefits such as improved tissue localization, minimized burst release, and controlled sequential drug release, by preserving the structural integrity of nanoparticles [25, 27, 28].

Hydrogels with high water content, tunable viscoelasticity, and biocompatibility have been intensively explored to enable topical delivery of bioactive molecules. Hydrogels are widely used for wound healing applications due to their similarity to the native ECM and ability to provide a moist environment. These multifunctional hydrogels can be fabricated with a wide range of functions and properties, including antibacterial, antioxidant, bioadhesive, and appropriate mechanical properties [29]. In a study, Bairagi et al. developed ferulic acid (FA) nanoparticles and studied their hypoglycemic wound healing activities. FA-loaded polymeric nanoparticles dispersion (oral administration) and FA-loaded polymeric nanoparticles-based hydrogel (topical administration) treated wounds were found to epithelize faster as compared with the diabetic wound control group. The hydroxyproline content increased significantly when compared with diabetic wound control. Results showed that FA significantly promotes wound healing in diabetic rats [30].

Metallic nanoparticles

Metallic nanocarriers have been extensively evaluated as suitable cargoes for biomedical applications. They have attained an exceptional position in the field of diagnosis, and drug delivery owing to their inimitable properties such as small size, very high surface area, capability for surface modification, and high reactivity towards living cells. Metallic nanoparticles such as AgNPs, AuNPs, and copper-based nanoparticles are widely used as therapeutic agents, primarily for their anti-infective and anti-inflammatory effects [21].

Silver nanoparticles

There is an unmet need for a novel antibiofilm approach and effective antimicrobial compounds, and silver nanotechnology-based therapeutics have captured the attention of health care providers for enhancing patient health care. AgNPs are used in clinical practice for a wide range of treatments such as burns, chronic ulcers, and diabetic wounds that have developed antibiotic resistance and hospital-acquired bacterial infection. In addition to anti-inflammatory effects, AgNPs treated wounds have shown abundant collagen deposition that could accelerate wound healing [23, 25]. AgNPs are the maximum studied nanoparticles in wound care management because of their known antibacterial effects [31]. The antibacterial effects of Ag are facilitated by the interaction of Ag^+ with three main constituents of the bacterial cell viz. (i) peptidoglycan composed cell wall, (ii) bacterial DNA, and (iii) proteins and enzymes involved in essential cellular processes such as electron transport chain (ETC). It also shows anti-inflammatory activity which promotes wound healing by reducing the release of cytokine, thereby, decreasing the infiltration of lymphocyte and mast cells.

In an investigation, Tsang et al. developed nanocrystalline silver (nAg) dressing which is on increase popularity-wise for treating DFU. Herein, it is shown that nAg alginate is potentially superior to MH and conventional dressing in healing DFUs in terms of ulcer size reduction rate [32]. In another research, Singla et al. prepared silver nanoparticles in the matrix of bamboo and examined cellulose nanocrystals for their ability to reduce inflammatory cytokines, oxidative stress and hasten the progress of healing events in the streptozotocin-induced diabetic mice model. These nano bio-composites showcased the potential to serve as highly effective and biocompatible DFU patients [33]. Later on, Almonaci Hernández et al., formulated AgNPs with antimicrobial properties. Daily topical administration of AgNPs solution with a metallic silver concentration of 1.8 mg/mL showed that such administration causes an improvement of the wound healing on average in less than 25 days of treatment [34]. Furthermore, Appapalam et al. formulated a phytofabricated nano-structured silver nanoparticle. They found that minimum bactericidal concentration (MBC) of AL-AgNPs (20 µg/mL) was highly effective against the studied multi antibiotic-resistant DFU isolates. The short-term exposures of DFU bacterial isolates with AL-AgNPs have displayed a remarkable growth inhibition, preformed biofilm disruption, enhanced intracellular ROS accumulation, increased membrane leakage, altered membrane integrity, and drastically ruptured membrane [35]. Thus, herein it is seen that

phytofabricated nano-structured silver could serve as the best antimicrobial agent for the eradication of infections in the diabetic wound. In a recent investigation, Li et al. developed a new Ag–ZnO loaded carboxymethyl cellulose/K-carrageenan/graphene oxide/konjac glucomannan (Ag–ZnOCGK) hydrogel clinical applications as wound-recuperating materials. The Ag–ZnO@CGK hydrogel indicated incredible swelling assimilation and impressive mechanical properties. Also, Ag–ZnO@CGK hydrogel exhibited great bactericidal movement against test microorganisms. *In vitro* viability testing demonstrated that fibroblast cells could endure well within the sight of Ag@CGK hydrogel, showing that Ag–ZnO@CGK hydrogel has great viability. *In vivo* animal models demonstrated that the Ag–ZnO@CGK hydrogel adequately quickened wound recuperation and histological examinations demonstrated advanced fibroblast development and quickened epithelialization. The test results demonstrated that Ag–ZnO@CGK hydrogel has incredible potential in advanced wound healing [36].

Gold nanoparticle

AuNPs have been widely studied for medical applications. Biocompatible AuNPs are biologically active materials that have potential medical applications in tissue regeneration, wound healing, and drug delivery. They inhibit lipid peroxidation and prevent reactive oxygen species and hence can reinstate the antioxidant imbalances [26]. The wound healing efficiency of AuNPs is operated at the phase of hemostasis and inflammation which is highly beneficial to DFUs. Several studies have reported the anti-oxidative and anti-hyperglycemic potential of AuNPs [28]. In a study, Yu et al., synthesized nerolidol functionalized gold nanoparticles (N-AuNPs) by the reduction of chloroauric acid. Their results-based N-AuNPs have delivered a novel therapeutic route for wound dressings in diabetic patients. AuNPs were found to be crystalline in nature, spherical in shape, and size in the range of 50–70 nm. The developed N-AuNPs based ointment showed an enhanced effect in the treatment of DFU [37]. In another study, Hernández Martínez et al. investigated gold nanocomposite functionalized with calreticulin that was found to promote clonogenicity of fibroblasts, keratinocytes, and accelerates the migration of fibroblasts [38].

Copper-based nanoparticles

CuNPs have also gained special attention in managing DFU infections. They are extremely small and have a high surface-to-volume ratio that can also serve as antifungal/antibacterial agents. These nanoparticles can promote wound healing by enhancing angiogenesis, re-epithelialization, matrix remodeling, and stabilization of collagen content [39]. In a research investigation, Goerne et al. prepared Cu/TiO_2-SiO_2 nanoparticles gel as an evident improvement in DFU cases. The prepared Cu/TiO_2-SiO_2 showed fabulous advantages in the healing of ulcers which indicates that it can be used as a primary apposite to stimulate the autolytic debridement on injures [40]. In another study, Xiao et al. prepared copper-based metal-organic framework nanoparticles incorporated with folic acid have been shown to induce angiogenesis, collagen deposition, and increased wound closure in diabetic mice [41]. In another study, López-Goerne et al. synthesized Cu/TiO_2–SiO_2 nanoparticles and embedded them in a polymeric gel matrix. The Cu/TiO2–SiO2 nanogel was used as conservative therapy for a chronic non-healing DFU on a 62-year-old female with several comorbidities and chronic complications of diabetes. Wound debridement was performed before nanogel administration. The nanogel was applied over the ulcer on alternate days initially for 2 weeks and then continued for 10 months. Significant improvement was observed in the wound healing process since the first application. The infection was limited and tissue regeneration was enhanced until the ulcer was completely healed. Cu/TiO2–SiO2 nanogel therapy enhanced reepithelialization and healing of the DFU. The successful outcome allowed to avoid the amputation that was proposed for the patient [39].

Inorganic Nanoparticles

Recent advances have shifted our focus to inorganic nanoparticles for specific targeting and control of their cellular actions. Being inorganic, they remain stable for long periods [42].

Inorganic NPs such as ZnO, TiO_2, CeO_2, and Y_2O_3 are a few most attractive options for DFU as they are comprised of essential mineral elements for the human body. ZnO nanoparticles (ZnO NPs) have exhibited therapeutic activities against melanoma, diabetes, bacterial infection, and inflammation, and have shown potential for wound healing applications. ZnO NPs have strong antibacterial properties and can stay at the wound site for a longer period, thus, are effectively used for wound healing. Zn reduces blood sugar levels by inhibiting glucose absorption and raising glucose absorption by skeletal muscles and adipose tissues [27, 28, 42].

Increased incidence of multi-drug resistance in microorganisms has become the greatest challenge in the treatment of DFU and urges the need for a new antimicrobial agent. In a study, Steffy et al. determined the bactericidal effects of ZnO NPs green synthesized from *Aristolochia indica* against Multi-drug Resistant Organisms (MDROs) isolated from pus samples of DFU patients attending a tertiary care hospital in South India. Minimum inhibitory concentration (MIC)/MBC assays were performed to determine bactericidal or bacteriostatic effects. Protein leakage and flow cytometric analysis confirmed bacterial cell death due to ZnO NPs [43]. In another research, Liu et al. synthesized zinc oxide nanoparticles (ZnO-NPs) using radish root (*Raphanus sativus)* extract. The produced ZnO-NPs display exceptional antibacterial activity towards microbes isolated from DFUs like *P. aeruginosa* ATCC 27853, MDR–*Escherichia coli*, *Staphylococcus aureus* ATCC 29213, MDR–MRSA, *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, MDR–*Pseudomonas aeruginosa*, and MDR *Acinetobacter baumannii*. These antibacterial ZnO-NPs further established the opportunity of developing wound dressing material for DFUs in nursing care [44].

Ceramic nanoparticles containing inorganic components have the fundamental therapeutic ability and can transport drugs to injury sites. CeO_2 is considered one of the most important options to be utilized for the treatment of DFU. Instead of bacteriostatic activity, they have antioxidant and auto regenerative abilities along with non-toxicity to neutrophils and macrophages [26]. CeO_2 NPs can scavenge free radicals and rescue cells from oxidative stress-induced cell death, and thus, be exploited in the healing of DFUs. CeO_2 NPs when conjugated with microRNA-146a enhanced the diabetic wound healing without impairing the biomechanical properties of the skin post healing [45]. Kobyliak et al. reported successful topical treatment of neuropathic DFUs with a novel gel containing CNPs. They investigated the ability of topical application of

cerium (Ce) dioxide nanoparticles (CNPs) to accelerate wound healing in an animal model and provide a rationale to develop this technology for use in humans affected by traumatic injury, diabetes, and burns. The CNPs have bacteriostatic activity, anti-inflammatory properties, can penetrate the wound tissue and reduce oxidative damage, therefore, protecting regenerative tissue, and suggesting its therapeutic potential for topical treatment of DFUs [46].

Short interference RNA (siRNA)-based nanoparticles

SiRNAs are artificially synthesized 19–23 nucleotide long double-stranded RNA molecules. RNA interference therapy permits the silencing of gene expression by targeting selective molecules in chronic wounds. Nanoparticle-based technology emerged as a strategy to protect the delivery of siRNA from degradation by intracellular RNases. Yan et al. developed collagen/GAG (Col/GAG) scaffolds activated by matrix metalloproteinase-9 (MMP-9)-targeting siRNA (siMMP-9) because the downregulation of the MMP-9 level *in situ* and the regeneration of impaired tissue are critical for improved DFU healing. Mixing the RALA cell-penetrating peptide with siMMP-9 led to the successful formation of the siMMP-9 complexes. The complexes were formulated at N: P ratios of 6–15, with a diameter of approximately 100–110 nm, and a positive zeta potential of about 40 mV, making them ideal for cellular uptake. The MMP-9 gene and protein level of M1 macrophages decreased by around 50 % and 30 % respectively in the scaffolds. The prepared formulation downregulated the MMP-9 gene and protein levels of human M1 macrophages by about 50-30 % respectively [47]. In another research, Kim and Yoo fabricated an MMP-2siRNA-incorporated linear polyethylenimine (LPEI) complex onto a nano-fibrous mesh in response to a high concentration of MMPs which accelerates the ulcers [48].

Lipid-based nanoparticles

In dermatology, lipid nanoparticles (LNPs) have received great attention from researchers due to their significant functionalities, greater adhesion to the skin, and film formation, enabling the hydration and maintenance of skin integrity, as well as more effective penetration through the skin barrier [49]. Lipid-based carriers are generally constituted from physiological lipids. Therefore, they are considered to be safe and free from toxicity. They liberate non-toxic moiety upon degradation and are well accepted for therapeutic purposes. Lipid-based nanocarriers are beneficial in many aspects such as controlled drug release, enhanced stability, biodegradability, drug targeting, increased drug load, and cost-effectiveness. In addition to being safe, are extensively used to deliver both hydrophilic and hydrophobic drugs.

Recent attention to nanostructured lipid carrier (NLC) research has proven their potential for the effective management of DFU [50]. Motawea et al. investigated the impact of topical phenytoin-loaded nanostructured lipid carriers in improving wound healing in patients with neuropathic DFUs. Twenty-seven patients with neuropathic DFUs were enrolled in this study. Patients were comparable in terms of size, grading of ulcer, and control of diabetes with no major deformity. All patients were managed by weekly sharp debridement if indicated and offloaded with cast shoes. They were equally categorized into three groups: phenytoin (PHT)-NLC-hydrogel (0.5 %w/v), phenytoin hydrogel (0.5 %w/v), and blank hydrogel groups. Changes in wound area were monitored over 2 months. Ulcers treated with PHT-NLC hydrogel showed smaller wound areas compared to control groups ($\rho < 0.05$). PHT-NLC hydrogel speeds up the healing process of the DFU without adverse effects when compared to the positive and negative control hydrogels [51].

Inefficient diabetic ulcer healing and scar formation remain a challenge worldwide, owing to a series of disordered and dynamic biological events that occur during the process of healing. A functional wound dressing that is capable of promoting ordered diabetic wound recovery is eagerly anticipated. Natarajan et al. developed a pio-nanostructured lipid carrier (Pio-NLC)-loaded collagen/chitosan (COL-CS) scaffold and evaluated it for its healing ability in diabetic wounds. The *in vitro* studies revealed that the Pio-NLC-COL-CS scaffold was biocompatible and enhanced cell growth compared with control and NLC-COL-CS. Using the streptozotocin-induced diabetic wound model, significantly ($p < 0.001$) higher rates of wound contraction in the Pio-NLC-COL-CS scaffold-treated group were observed in comparison with that in the control and NLC-COL-CS-treated group. Later on, Sun et al., designed a silicone elastomer with embedded 20(S)-protopanaxadiol-loaded nanostructured lipid carriers (PPD-NS) to achieve ordered recovery in scarless diabetic ulcer healing. The PPD-NS showed excellent *in vitro* anti-inflammatory and proangiogenic activity. Moreover, in diabetic mice with full-thickness skin excision wounds, treatment with PPD-NS significantly promoted *in vivo* scarless wound healing by suppressing inflammatory infiltration in the inflammatory phase, promoting angiogenesis during the proliferation phase, and regulating collagen deposition in the remodeling phase [52].

Nanofibers

Nanofibers have received much attention because of their structural similarity, which closely mimics the native ECM environment. Nanofibers promote wound healing by providing characteristics of high surface area to volume ratio, tunable mechanical properties, increased porosity, and ability to encapsulate nanoparticles and bioactive compounds for controlled release, which can support the cells to actively interact with the matrix during functionalization and remodeling [53]. Nanofibers could be a wonderful candidate for the DFU treatment with so many benefits. Huge porosity, excellent humidity absorption, a better oxygen exchange rate, and some antibacterial activities make it a suitable dosage form for the treatment of DFU [53].

Nanofibrous scaffolds are promising platforms for wound healing, especially due to their similarity to the extracellular matrix (ECM) and their capability to promote cell adhesion and proliferation and to restore skin integrity when grafted into the wound site [54]. Assi et al. hypothesized that delivery of mesenchymal stem cells (MSCs) in a biomimetic collagen scaffold improves diabetic ulcers. Rolled scaffolds were hypoxic, inducing MSC synthesis and secretion of vascular endothelial growth factor (VEGF). Diabetic mice with wounds treated with rolled scaffolds containing MSCs showed increased healing compared to those in controls. Increased cellular proliferation, increased VEGF expression and capillary density, and increased numbers of macrophages, fibroblasts, and smooth muscle cells were observed during histologic examination. With the addition of laminin to the collagen scaffold, the aforesaid ef-

fects were enhanced [55]. Later on. Goonoo and Bhaw-Luximon observed polymeric nanofibrous translational chronic wound healing. Research showed that the three-dimensional (3D) scaffold more closely mimics the biochemical-mechanical milieu of wounds and advancing knowledge of cell biology had led to the next generation of engineered biopolymeric nano scaffolds; this has paved the way towards personalized wound care as they can address multiple requirements of skin physiology [53].

Furthermore, Zheng et al. prepared collagen-based dressings for the delivery of neurotensin (NT), a neuropeptide that acts as an inflammatory modulator in wound healing. The performance of NT alone and NT-loaded collagen matrices to treat wounds in STZ diabetic induced mice was evaluated. Results showed that the prepared dressings were not-cytotoxic up to 72 h after contact with macrophages (Raw 264.7) and human keratinocyte (HaCaT) cell lines. Moreover, those cells were shown to adhere to the collagen matrices without a noticeable change in their morphology [56]. Liu et al. developed electrospun nanofibers as a wound dressing for treating DFUs by electrospinning with huge porosity, excellent humidity absorption, a better oxygen exchange rate, and some antibacterial activities. They laid much emphasis on the present techniques which are applied in the fabrication of nanofibrous dressing that utilizes a variety of materials and active agents to offer better health care for the patients suffering from DFU [57].

Moreover, Samadian et al. prepared functional wound dressing for DFU management and treatment of DFU. Cellulose Acetate/Gelatin (CA/Gel) electrospun mat loaded with berberine (Beri) was fabricated as the DFU-specific wound dressing. The wound healing efficacy of the fabricated dressings was evaluated in streptozotocin-induced diabetic rats. The antibacterial evaluations demonstrated that the dressings exhibited potent antibacterial activity. The collagen density and the angiogenesis score obtained in the animal studies indicated proper wound healing. These findings implied that the incorporation of berberine did not compromise the physical properties of dressing while improving the biological activities [58]. Li et al. developed bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair. The study displayed prominent multifunctional properties and angiogenic capacity of PABC hydrogel scaffolds which enable their promising applications in angiogenesis-related regenerative medicine [59]. In a subsequent study, Roy et al. developed a flexible screenprinted wound dressing employing a nanocomposite hybrid for the selective detection and quantification of *S. aureus* target DNA which is responsible for slow or non-healing DFUs [60].

Near-infrared (NIR)-responsive black phosphorus (BP)-based gel

Current therapeutic approaches for diabetic ulcers primarily focus on injury debridement, reducing microbial infiltration, weight control, and patient training. These medicines can offer some relief from discomfort and may assist with forestalling contamination. Nevertheless, their impact on speeding up injury mending is minor. The therapy of diabetic ulcers remains a significant clinical challenge because of the intricate injury recuperating milieu that highlights constant injuries, hindered angiogenesis, relentless torment, bacterial diseases, and exacerbated irritation. An exceptional technique was created by Ouyang et al., 2020 that successfully focuses on this multitude of issues. The examination discusses a BP-based gel with the qualities of fast arrangement and NIR responsiveness to resolve these issues. The *in situ* showered BP-based gel could go about as a brief, biomimetic "skin" to briefly protect the tissue from the external climate and speed up constant injury recuperation by advancing the expansion of endothelial cells, vascularization, and angiogenesis and a medication "repository" to store helpful BP and agony diminishing lidocaine hydrochloride (Lid). With a few minutes of NIR laser illumination, the BP-based gel produces local heat to speed up the microcirculatory bloodstream, intercede the arrival of stacked Lid for "on request" help with discomfort, dispose of microscopic organisms, and reduce irritation. This original methodology not just presents an idea of *in situ* sprayed, NIR-responsive discomfort relieving gel focusing on the difficult injury recuperating milieu in diabetes but additionally gives a proof-of-idea utilization of BP-based materials in DU treatment [61].

Clinical outcomes

Preclinical studies have shown promising results in improving wound healing using a variety of agents for promoting tissue healing, including growth factors, small molecules, and siRNA-based therapies. Despite recent technological advances, challenges in retaining and extending their therapeutic effect in the harsh wound environment have limited the pace for clinical implementation [62]. To overcome this limitation, nanoparticle formulations, nanofiber scaffolds, and hydrogel-related treatments are being developed [21, 22]. Many clinical trials have been conducted on the use of AgNPs for wound healing, particularly burns and chronic wounds (diabetic wounds). Currently, some dressings available in the market contain AgNPs [63]. The most successful polymer for fabricating polymeric nanoparticles is PLGA, which is approved for clinical use in humans as a DDS by the FDA [64]. Clinical trials have shown that recombinant human-platelet-derived growth factor, the only FDA-approved growth factor available for clinical use, increases the likelihood of wound closure and decreases the time to heal the wound completely [65]. As of now, the only siRNA delivery depot waiting for approval is the siG12D LODER therapeutic to combat non-resectable pancreatic dual adenocarcinoma [66]. Several wound bandage materials that are effective in promoting skin regeneration have been introduced to the market. Inorganic-based Au, copper, ZnO, cerium oxide, and silica nanoparticles are still under clinical investigation [67].

Conclusion

DFU is one of the major complications of diabetes, representing a leading cause of hospitalization and non-traumatic lower-limb amputations. The major risk factors which prevent the healing process of DFUs are diabetic neuropathy, peripheral vascular diseases, and abnormal immune responses. The physiology of the healing process is perturbed in the case of DFU by both internal and external factors, such as altered cellular and cytokines response, poor vascularization, and infection by microorganisms. The use of nanotechnology as a treatment for diabetic wound healing is growing exponentially. The research and development efforts in this area will have a significant impact on the treatment of wound regener-

ation, especially chronic wounds, which present a significant burden to the quality of life and the healthcare system. Nanotechnology-based remedies are likely to represent the next frontier in the pursuit of therapeutic breakthroughs in chronic wound healing.

Acknowledgments

The authors are thankful to the Faculty of Pharmacy, Integral University for providing all the necessary facilities related to the present work (Manuscript Communication Number: IU/R&D/2021-MCN0001307).

Conflict of Interest

The authors declare that they have no conflict of interest

References

[1] Ansari MA, Ali K, Farooqui Z et al. Nanotechnology and Diabetic Foot Ulcer: Future Prospects. In: Zubair M, Ahmad J, Malik A, Talluri MR, eds. Diabetic foot ulcer. Singapore: Springer; 2021. doi:10.1007/978-981-15-7639-3_20

[2] Oguntibeju OO. Medicinal plants and their effects on diabetic wound healing. Vet World 2019; 12: 653

[3] Greaves NS, Ashcroft KJ, Baguneid M et al. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. J Dermatol Sci 2013; 72: 206–217

[4] Moeini M, Shahriari M, Yousefi H et al. An investigation on the wound severity and its association with predisposing factors in patients with diabetic foot. J Clin Nurs Midwifery 2017; 5: 67–75

[5] Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci 2018; 1411: 153–165

[6] Basu S, Yudkin JS, Kehlenbrink S et al. Estimation of global insulin use for type 2 diabetes, 2018–30: a microsimulation analysis. Lancet Diabetes Endocrinol 2019; 7: 25–33

[7] Behl T, Grover M, Shah K et al. Role of Omega-3-Fatty Acids in the Management of Diabetes and Associated Complications. In: Watson RW, Preedy RV, eds. Bioactive food as dietary interventions for diabetes. Academic Press; 2019: 185–192

[8] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87: 4–14

[9] Whiting DR, Guariguata L, Weil C et al. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94: 311–321

[10] Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World J Diabetes 2015; 6: 37–53

[11] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018; 14: 88–98

[12] Alavi A, Sibbald RG, Mayer D et al. Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol 2014; 70: 1–e1

[13] Farahani RM, Kloth LC. The hypothesis of 'biophysical matrix contraction': Wound contraction revisited. Int Wound J 2008; 5: 477–482

[14] Ezhilarasu H, Vishalli D, Dheen ST et al. Nanoparticle-based therapeutic approach for diabetic wound healing. Nanomaterials 2020; 10: 1234

[15] Sindhu S. An overview on diabetic foot ulcer (DFU): Mini review. Diabetes Case Rep 2018; 3: 134. doi:10.4172/2572-5629.1000134

[16] Pouget C, Dunyach-Remy C, Pantel A et al. Biofilms in diabetic foot ulcers: Significance and clinical relevance. Microorganisms 2020; 8: 1580

[17] Lavery LA, Bhavan K, Wukich DK. Biofilm and diabetic foot ulcer healing: All hat and no cattle. Ann Transl Med 2019; 7: 159. doi:10.21037/atm.2019.03.33.

[18] Yang S, Hu L, Han R et al. Neuropeptides, inflammation, biofilms, and diabetic foot ulcers. Exp Clin Endocrinol Diabetes 2021. doi:10.1055/a-1493-0458.

[19] Afonso AC, Oliveira D, Saavedra MJ et al. Biofilms in diabetic foot ulcers: Impact, risk factors and control strategies. Int J Mol Sci 2021; 22: 8278. doi:10.3390/ijms22158278

[20] Dowd SE, Wolcott RD, Sun Y et al. Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP). PLoS One 2008; 3: e3326

[21] Ch'ng JH, Chong KK, Lam LN et al. Biofilm-associated infection by enterococci. Nat Rev Microbiol 2019; 17: 82–94

[22] Chellappan DK, Yenese Y, Wei CC et al. Nanotechnology and diabetic wound healing: A review. Endocr Metab Immune Disord Drug Targets 2017; 17: 87–95

[23] Santema TB, Poyck PP, Ubbink DT. Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: Highlights of a Cochrane systematic review. Wound Repair Regen 2016; 24: 737–744

[24] Dixon D, Edmonds M. Managing diabetic foot ulcers: Pharmacotherapy for wound healing. Drugs 2021; 81: 29–56

[25] Hussain Z, Thu HE, Shuid AN et al. Recent advances in polymer-based wound dressings for the treatment of diabetic foot ulcer: An overview of state-of-the-art. Curr Drug Targets 2018; 19: 527–550

[26] Zare H, Rezayi M, Aryan E et al. Nanotechnology-driven advances in the treatment of diabetic wounds. Biotechnol Appl Biochem 2021; 68: 1281–1306. doi:10.1002/bab.2051

[27] Bernal-Chávez S, Nava-Arzaluz MG, Quiroz-Segoviano RI et al. Nanocarrier-based systems for wound healing. Drug Dev Ind Pharm 2019; 45: 1389–1402

[28] Vellayappan MV, Jaganathan SK, Manikandan A. Nanomaterials as a game changer in the management and treatment of diabetic foot ulcers. RSC Adv 2016; 6: 114859–114878

[29] Asadi N, Pazoki-Toroudi H, Del Bakhshayesh AR et al. Multifunctional hydrogels for wound healing: Special focus on biomacromolecular based hydrogels. Int J Biol Macromol 2021; 170: 728–750

[30] Bairagi U, Mittal P, Singh J et al. Preparation, characterization, and *in vivo* evaluation of nano formulations of ferulic acid in diabetic wound healing. Drug Dev Ind Pharm 2018; 44: 1783–1796

[31] Almonaci Hernández CA, Juarez-Moreno K, Castañeda-Juarez ME et al. Silver nanoparticles for the rapid healing of diabetic foot ulcers. Int J Med Nano Res 2017; 4: 019. doi:10.23937/2378-3664/1410019

[32] Tsang KK, Kwong EW, To TS et al. A pilot randomized, controlled study of nanocrystalline silver, manuka honey, and conventional dressing in healing diabetic foot ulcer. Evid Based Complement Alternat Med: Ecam 2017; 2017: 5294890. doi:10.1155/2017/5294890.

[33] Singla R, Soni S, Kulurkar PM et al. *In situ* functionalized nanobiocomposites dressings of bamboo cellulose nanocrystals and silver nanoparticles for accelerated wound healing. Carbohydr Polym 2017; 155: 152–162

[34] Almonaci Hernández CA, Juarez-Moreno K, Castañeda-Juarez ME et al. Silver nanoparticles for the rapid healing of diabetic foot ulcers. Int. J. Med. Nano Res 2017; 4: 2378–3664

[35] Appapalam ST, Paul B, Arockiasamy S et al. Phytofabricated silver nanoparticles: Discovery of antibacterial targets against diabetic foot ulcer derived resistant bacterial isolates. Mater Sci Eng C 2020; 117: 111256

[36] Li XX, Dong JY, Li YH et al. Fabrication of Ag–ZnO@ carboxymethyl cellulose/K-carrageenan/graphene oxide/konjac glucomannan hydrogel for effective wound dressing in nursing care for diabetic foot ulcers. Appl Nanosci 2020; 10: 729–738

[37] Yu J, Wang X, Li Y et al. Synthesis of nerolidol functionalized gold nanoparticles for wound regeneration in people with diabetic foot ulcers in nursing care management. Sci Adv Mater 2018; 10: 1775–1781

[38] Hernández Martínez SP, Rivera González TI, Franco et al. A novel gold calreticulin nanocomposite based on chitosan for wound healing in a diabetic mice model. Nanomaterials 2019; 9: 75. doi: 10.3390/nano9010075

[39] López-Goerne T, Ramírez-Olivares P, Pérez-Dávalos LA et al. Catalytic nanomedicine. Cu/TiO2–SiO2 nanoparticles as treatment of diabetic foot ulcer: a case report. Curr Nanomed 2020; 10: 290–295

[40] Goerne TL, Arévalo A, Ramírez P et al. Copper nanoparticles as treatment of diabetic foot ulcers: A case report. Glob Adv Res J Med Med Sci 2017; 6: 267–270

[41] Xiao J, Zhu Y, Huddleston S et al. Copper metal–organic framework nanoparticles stabilized with folic acid improve wound healing in diabetes. ACS Nano 2018; 12: 1023–1032

[42] Gupta S, Bansal R, Gupta S et al. Nanocarriers and nanoparticles for skin care and dermatological treatments. Indian Dermatol Online J 2013; 4: 267–272. doi:10.4103/2229-5178.120635

[43] Steffy K, Shanthi G, Maroky AS et al. Enhanced antibacterial effects of green synthesized ZnO NPs using *Aristolochia indica* against Multi-drug resistant bacterial pathogens from Diabetic Foot Ulcer. J Infect Public Health 2018; 11: 463–471

[44] Liu D, Liu L, Yao L et al. Synthesis of ZnO nanoparticles using radish root extract for effective wound dressing agents for diabetic foot ulcers in nursing care. J Drug Deliv Sci Technol 2020; 55: 101364

[45] Zgheib C, Hilton SA, Dewberry LC et al. Use of cerium oxide nanoparticles conjugated with microRNA-146a to correct the diabetic wound healing impairment. J Am Coll Surg 2019; 228: 107–115

[46] Kobyliak N, Abenavoli L, Kononenko L et al. Neuropathic diabetic foot ulcers treated with cerium dioxide nanoparticles: A case report. Diabetes Metab Syndr 2019; 13: 228–234

[47] Yan LP, Castaño IM, Sridharan R et al. Collagen/GAG scaffolds activated by RALA-siMMP-9 complexes with potential for improved diabetic foot ulcer healing. Mater Sci Eng C 2020; 114: 111022

[48] Kim HS, Yoo HS. *In vitro* and *in vivo* epidermal growth factor gene therapy for diabetic ulcers with electrospun fibrous meshes. Acta Biomaterialia 2013; 9: 7371–7380

[49] De Souza ML, Dos Santos WM, de Sousa ALMD et al. Lipid nanoparticles as a skin wound healing drug delivery system: discoveries and advances. Curr Pharm Des 2020; 26: 4536–4550

[50] Natarajan J, Sanapalli BKR, Bano M. Nanostructured lipid carriers of pioglitazone loaded collagen/chitosan composite scaffold for diabetic wound healing. Adv Wound Caref 2019; 8: 499–513

[51] Motawea A, Abd El-Gawad AEH, Borg T et al. The impact of topical phenytoin loaded nanostructured lipid carriers in diabetic foot ulceration. Foot (Edinb) 2019; 40: 14–21

[52] Sun D, Guo SY, Yang L et al. Silicone elastomer gel impregnated with 20(S)-protopanaxadiol-loaded nanostructured lipid carriers for ordered diabetic ulcer recovery. Acta Pharmacol Sin 2020; 41: 119–128

[53] Goonoo N, Bhaw-Luximon A. Analyzing polymeric nanofibrous scaffold performances in diabetic animal models for translational chronic wound healing research. Nanotechnol Rev 2017; 6: 583–600

[54] Ruggeri M, Bianchi E, Rossi S et al. Nanotechnology-based medical devices for the treatment of chronic skin lesions: from research to the clinic. Pharmaceutics 2020; 12: 815. doi:10.3390/pharmaceutics 12090815

[55] Assi R, Foster TR, He H et al. Delivery of mesenchymal stem cells in biomimetic engineered scaffolds promotes healing of diabetic ulcers. Regen Med 2016; 11: 245–260

[56] Zheng Z, Liu Y, Huang W et al. Neurotensin-loaded PLGA/CNC composite nanofiber membranes accelerate diabetic wound healing. Artif Cells Nanomed Biotechnol 2018; 46: 493–501

[57] Liu Y, Zhou S, Gao Y et al. Electrospun nanofibers as a wound dressing for treating diabetic foot ulcer. Asian J Pharm Sci 2019; 14: 130–143

[58] Samadian H, Zamiri S, Ehterami A et al. Electrospun cellulose acetate/gelatin nanofibrous wound dressing containing berberine for diabetic foot ulcer healing: *In vitro* and *in vivo* studies. Sci Rep 2020; 10: 1–2

[59] Li Y, Xu T, Tu Z et al. Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair. Theranostics 2020; 10: 4929

[60] Roy S, Bisaria K, Nagabooshanam S et al. An electroanalytical paper-based wound dressing using ZIF-67/C 3 N 4 nanocomposite towards the monitoring of *staphylococcus aureus* in diabetic foot ulcer. IEEE Sens J 2020; 21: 1215–1221

[61] Ouyang J et al. *In situ* sprayed NIR-responsive, analgesic black phosphorus-based gel for diabetic ulcer treatment. Proc Natl Acad Sci U S A 2020; 117: 28667–28677

[62] Layliev J, Wilson S, Warren SM et al. Improving wound healing with topical gene therapy. Adv Wound Care 2012; 1: 218–223

[63] Naderi N, Karponis D, Mosahebi A et al. Nanoparticles in wound healing; from hope to promise, from promise to routine. Front Biosci 2018; 23: 1038–1059

[64] Gunatillake PA, Adhikari R. Biodegradable synthetic polymers for tissue engineering. Eur Cell Mater 2003; 5: 1–16

[65] Li W, Tsen F, Sahu D et al. Extracellular Hsp90 (eHsp90) as the actual target in clinical trials: Intentionally or unintentionally. Int Rev Cell Mol Biol 2013; 303: 203–235

[66] Nethi SK, Das S, Patra CR et al. Recent advances in inorganic nanomaterials for wound-healing applications. Biomater Sci 2019; 7: 2652–2674

[67] Hamdan S, Pastar I, Drakulich S et al. Nanotechnology-driven therapeutic interventions in wound healing: Potential uses and applications. ACS Cent Sci 2017; 3: 163–175