

Targeting oxidative damage in diabetic foot ulcers: integrative strategies involving antioxidant drugs and nanotechnologies

Runze Wang¹, Bowen Li², Mengchao Dong³, Huili Zhu^{4,*}, Ping Jin^{5,*}, Yingying Zou^{1,6,*}

¹Department of Pathology and Pathophysiology, School of Basic Medicine, Kunming Medical University, No. 1168, Chunrong West Road, Yuhua Street, Chenggong District, Kunming 650500, China

²State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, and West China School of Basic Medical Sciences and Forensic Medicine, Sichuan University, and Collaborative Innovation Center for Biotherapy, No. 17 People's South Road, Chengdu 610041, China

³Department of Orthopedics, The First Affiliated Hospital of Zhengzhou University, No. 1, Jianshe East Road, Erqi District, Zhengzhou 450052, China

⁴Department of Reproductive Medicine, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital of Sichuan University, No. 20 People's South Road, Chengdu 610041, China

⁵State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, School of Life Sciences, Yunnan University, East Outer Ring South Road, Chenggong District, Kunming, Yunnan, China

⁶Frontiers Medical Center, Tianfu Jincheng Laboratory, Intersection of Hexiang 1st Street and Xinchuan Road, Shuangliu District, Chengdu 610095, China

*Corresponding authors. Yingying Zou, E-mail: zouyingying@kmmu.edu.cn; Ping Jin, E-mail: jinp533023@163.com

Abstract

Foot ulcerations in patients with diabetes are common and severe, typically caused by infection and chronic inflammation. Poor blood circulation and neuropathy impair the body's ability to heal wounds effectively, creating a conducive environment for ulcers. Excessive reactive oxygen species contribute to ulcer development by damaging cellular structures and hindering wound healing. The administration of antioxidants can protect cells from oxidative damage and promote wound recovery. Antioxidants such as epidermal growth factors, flavonoid hesperidin, alpha-lipoic acid, and N-acetylcysteine effectively reduce oxidative stress. Encapsulating various drugs into nanoparticles and targeting carriers such as hydrogels, metal-organic frameworks, and nanohydrogels can improve their therapeutic effects. Nanotechnologies have been shown to boost tissue regeneration by modifying biomaterial properties, modulating signal release, and targeting key factors. Here, we describe the occurrence and development of diabetic foot ulcers (DFUs), emphasizing the role of oxidative damage in these processes. This review summarizes the strategy for targeting oxidative damage in DFUs using nanotechnology-loaded antioxidant drugs. This review advocates for the use of personalized biomaterials in treating DFUs and provides a theoretical basis for their potential clinical and translational applications.

Keywords: Diabetes; Oxidative stress; Antioxidant treatment; Diabetic foot ulcers; Wound healing; Inflammation

Highlights

- DFUs are prevalent and severe, primarily caused by infection, chronic inflammation, and impaired wound healing due to poor circulation and neuropathy.
- Excessive reactive oxygen species (ROS) contribute to DFU development by damaging cells and hindering wound healing.
- Antioxidants like EGF, hesperidin, ALA, and N-acetylcysteine effectively reduce oxidative stress and enhance wound recovery.
- Nanotechnology-loaded antioxidants offer a promising approach for personalized treatment of DFUs by targeting oxidative damage.

Background

Diabetes mellitus (DM), a chronic metabolic disorder caused by insufficient insulin, or insulin resistance [1], poses a significant global public health challenge [2]. As of 2021, over 529 million people worldwide had diabetes, contributing to 6.7 million deaths annually [3, 4]. This number is projected to increase to ~700 million by 2045 [5]. DM is characterized by elevated glucose levels and protein glycosylation [6], which lead to oxidative stress, microvascular and nerve damage, and immune dysfunction, thereby aggravating diabetic complications [7]. A severe complication of DM is diabetic foot ulcers (DFUs), which are a major global health concern. DFUs result from nerve and blood vessel damage, leading to sensory

loss and poor wound healing [8]. Minor foot injuries can progress into deep, infection-prone ulcers, often requiring amputation as infections spread to underlying tissues and bones [9]. Approximately 25% of individuals with diabetes experience complications from chronic wounds, leading to significant pain, reduced quality of life, and an increased mortality risk [10–12]. Without timely intervention, DFUs can lead to soft tissue infection, necrosis, and peripheral arterial disease, with nearly half of all ulcers becoming infected and many progressing to amputation [13, 14]. The financial and societal burden of DFUs is substantial, with treatment costs reaching billions of dollars annually [15, 16]. Aging populations, rising healthcare expenses, and the increasing

Received: December 31, 2024. Revised: February 21, 2025. Accepted: February 27, 2025

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prevalence of diabetes further complicate the management of chronic wounds. Addressing DFUs through efficient, cost-effective strategies is essential to prevent severe complications, reduce mortality rates, and improve patient outcomes [17].

Oxidative stress plays a crucial role in the development and persistence of diabetic wounds by creating a chronic inflammatory microenvironment. Hyperglycemia in patients with diabetes promotes the formation of advanced glycation end products (AGEs), which bind to their receptors (RAGE) and activate signaling pathways that enhance reactive oxygen species (ROS) production [10, 18]. Additionally, hyperglycemia induces mitochondrial dysfunction and electron leakage in the electron transport chain, further increasing ROS levels [19]. Chronic inflammation in foot ulcers activates neutrophils and macrophages, which produce substantial ROS while engulfing pathogens and clearing necrotic tissue [20]. Furthermore, patients with diabetes exhibit impaired antioxidant system functions, including reduced glutathione (GSH) levels, resulting in a compromised ability to scavenge ROS [21]. Excess ROS can destroy cellular integrity and function by oxidizing proteins, lipids, and deoxyribonucleic acid (DNA), thereby hindering wound healing [22, 23]. ROS can also oxidize DNA bases, causing mutations and cellular dysfunction. Oxidative stress exacerbates insulin resistance, a critical barrier to wound healing [24]. Oxidative stress activates stress kinases such as JNK, which phosphorylate IRS-1 and inhibit insulin signaling. Simultaneously, ROS activate nuclear factor kappa B (NF- κ B) and pro-inflammatory cytokines, promoting the release of pro-inflammatory mediators such as TNF- α and IL-6 [16, 25–27]. Elevated levels of these mediators in patients with diabetes are closely linked to insulin resistance and delayed wound healing, perpetuating the chronicity of diabetic wounds.

To address the harmful effects of oxidative stress on wound healing in diabetes, various strategies involving antioxidant interventions have been developed. These approaches aim to decrease ROS production and prevent oxidative damage to cells, thereby promoting efficient wound repair [28]. Commonly used antioxidants include N-acetylcysteine, traditional Chinese medicine (TCM) monomers such as resveratrol, and growth factors such as VEGF [29]. Emerging antioxidant treatments, including bioactive plant compounds and innovative antioxidant nanomedicines, offer promising avenues for improving diabetic wound healing. These strategies aim to accelerate wound repair and also improve the overall quality of life of affected individuals. Continued research on the effectiveness of these interventions could yield novel approaches to manage and treat diabetic wounds more effectively [30, 31].

This review explores the latest evidence on the causes, mechanisms, and management of DFUs, specifically focusing on oxidative modulation theory. By unraveling the underlying factors driving DFU development, healthcare professionals can better tailor treatment strategies to address the specific needs of affected individuals [32]. Early intervention and holistic care are crucial for reducing the severe complications and long-term impacts associated with DFUs [33].

Review

Pathological characteristics of diabetic foot ulcers

Diabetic foot is a severe complication of diabetes characterized by chronic inflammation, neuropathy, vasculopathy, and an impaired immune response, often resulting in chronic ulcers and infections. Chronic inflammation is a significant

pathological characteristic of DFUs. The elevation of pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6, contributes to a prolonged inflammatory phase in the wound healing process [26]. Concurrently, macrophage polarization in DFUs is disrupted, with an excess of M1 macrophages releasing ROS and inflammatory mediators, thereby hindering the transition to M2 macrophages, which facilitate tissue repair [34, 35].

Diabetic peripheral neuropathy (DPN) is categorized as sensory or motor neuropathy. Sensory neuropathy may result in painless feet, while motor nerve damage can lead to Charcot arthropathy. The typical manifestations of DPN include decreased sensory nerve action potential amplitude, slowed sensory nerve conduction velocity, decreased compound muscle action potential amplitude, and slowed motor nerve conduction velocity [36].

Diabetes-related vascular alterations, including atherosclerosis and microangiopathy, contribute to microvascular dysfunction, peripheral arterial disease, and impaired perfusion. This impairment, coupled with reduced blood flow and capillary rarefaction, exacerbates ischemia, hypoxia, and necrosis, ultimately delaying healing. In addition, an impaired immune response is a pathological characteristic of diabetes. High blood sugar levels impair neutrophil and macrophage function, thereby weakening the body's ability to control infections. This is particularly evident in patients with diabetes-related foot infections [37].

Diabetic foot wounds exhibit reduced expression of critical growth factors, which impedes wound closure and delays re-epithelialization [38]. Excessive activity of matrix metalloproteinases (MMPs) degrades extracellular matrix (ECM) proteins, preventing the formation of stable granulation tissue [39]. Impaired ECM deposition results in the abnormal expression of growth factors such as TGF- β and reduced platelet-derived growth factor levels in chronic wound conditions. This negatively affects fibroblast activity, keratinocyte migration, and angiogenic tissue remodeling [40].

Oxidative stress plays a critical role in the pathogenesis of diabetic foot disease by contributing to tissue damage, impaired healing, and chronic inflammation. Chronic hyperglycemia induces oxidative stress, damaging DNA, proteins, and lipids and further elevating oxidative stress levels. This cascade can lead to vascular dysfunction, impaired angiogenesis, tissue damage, and increased bacterial colonization [41]. For example, research indicates that intense oxidative stress in the footpads of diabetic mice after *Candida albicans* infection activates the NF- κ B protein complex, triggering pyroptosis and apoptosis through the NLRP3 inflammasome. This contributes to the severity of skin infections and suggests NLRP3 inflammasomes as potential therapeutic targets [42]. A recent study found that reduced expression of microRNA-146a (miR-146a) in patients with type 2 DM and severe DFUs is linked to increased oxidative and endoplasmic reticulum (ER) stress, highlighting miR-146a as a potential therapeutic target for managing DFU progression. These results indicate that oxidative stress is a key pathological feature of diabetic foot disease. Targeting oxidative stress is an effective strategy for managing diabetic foot disease.

The formation and progression of diabetic foot ulcers

The formation of DFUs arises from the complex interplay of multiple factors, with peripheral neuropathy and peripheral vascular disease being the primary contributors [8]. Nerve

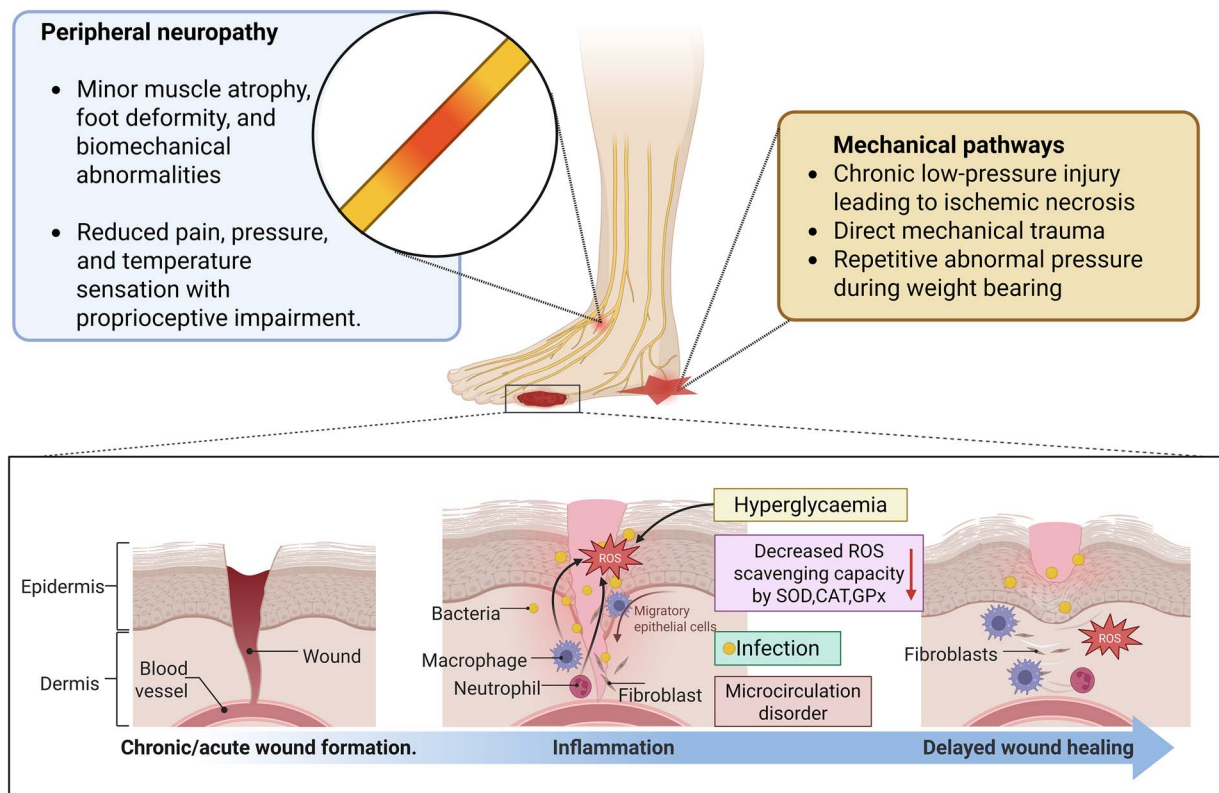


Figure 1. Pathways are involved in the development of DFUs. Neuropathy is a crucial factor in the development of DFUs. Sensory neuropathy leads to the loss of protective sensation, whereas autonomic neuropathy causes changes in the viscoelastic properties of the skin, such as dryness. These alterations, combined with external mechanical factors, can result in subcutaneous hemorrhage and even full-thickness ulcers. Other mechanisms contributing to the development of DFUs include sustained low pressure or extremely high pressure, such as direct mechanical injury from sharp objects. Hyperglycemia, decreased local wound ROS scavenging capacity, infection, and microcirculatory disorders can all contribute to delayed wound healing once an ulcer occurs. *GPx* glutathione peroxidase, *DFUs* diabetic foot ulcers, *ROS* reactive oxygen species

damage caused by hyperglycemia in the early stages of diabetic foot disease can activate destructive metabolic pathways, such as the polyol and hexosamine pathways, through oxidative stress. This aggravates peripheral neuropathy, damages sensory nerves, and reduces the foot's perception of pain, pressure, and temperature, thereby increasing the risk of unnoticed damage and ulceration [43, 44]. Concurrently, atherosclerosis and microcirculation disorders caused by peripheral vascular disease lead to insufficient blood supply to the limbs, tissue hypoxia, and malnutrition, which hinder wound healing [34, 45]. Oxidative stress can also damage endothelial cells, reduce the bioavailability of nitric oxide, impede angiogenesis, and exacerbate vascular dysfunction [46, 47].

In the early stages of diabetic foot development, nerve dysfunction and dry skin make individuals prone to skin cracks, lesions, and small wounds. By the mid-stage, these small wounds can deepen into ulcers and expand, affecting the skin, subcutaneous tissue, and even muscles and bones [22, 48]. The spread of the infection can exacerbate this condition, leading to an inflammatory response and tissue necrosis. The inflammation can escalate, resulting in abscess formation and tissue destruction. In the advanced stages, diabetic foot may develop dry or wet gangrene, and the infection may extend to the bone, causing osteomyelitis. In critical cases, bacteria can enter the bloodstream, leading to a systemic infection [49]. If the infection in the end-stage diabetic foot cannot be controlled or if gangrene becomes severe, amputation may be required to prevent its further spread [50]. Post-amputation

complications may include infection, thrombosis, chronic pain, and psychological distress [51, 52] (Figure 1).

Diabetic peripheral neuropathy

DPN is a prevalent complication affecting over half of the diabetic population, encompassing both type 1 and type 2 diabetes [53, 54]. DPN is a comprehensive term that includes diabetic sensory neuropathy and diabetic motor neuropathy as primary manifestations. Oxidative stress is a pivotal factor in the pathogenesis of DPN and exerts detrimental effects on nerve cells [55]. It activates the AGE and protein kinase C (PKC) pathways, orchestrates lipid peroxidation, and enhances the expression of inflammatory mediators such as transforming growth factor β (TGF- β) and interleukin-1 (IL-1) [56, 57]. These actions culminate in nerve cell injury and sensory nerve impairment, diminishing pain sensation and consequently leading to unnoticed tissue damage [47]. Insensitivity to pain in patients with foot ulcers can lead to the neglect of painful injuries, potentially worsening the ulcers. This diminished perception may result in unnoticed injuries, infections, and, in severe cases, amputations, which are major contributors to non-traumatic lower-limb amputations in many high-income nations. Furthermore, DPN in both sensory and motor forms is the second most frequent cause of post-traumatic nerve damage, affecting various peripheral nerves, including those responsible for pain sensation, motor function, and autonomic regulation [58, 59]. Managing oxidative stress using antioxidants and other therapeutic

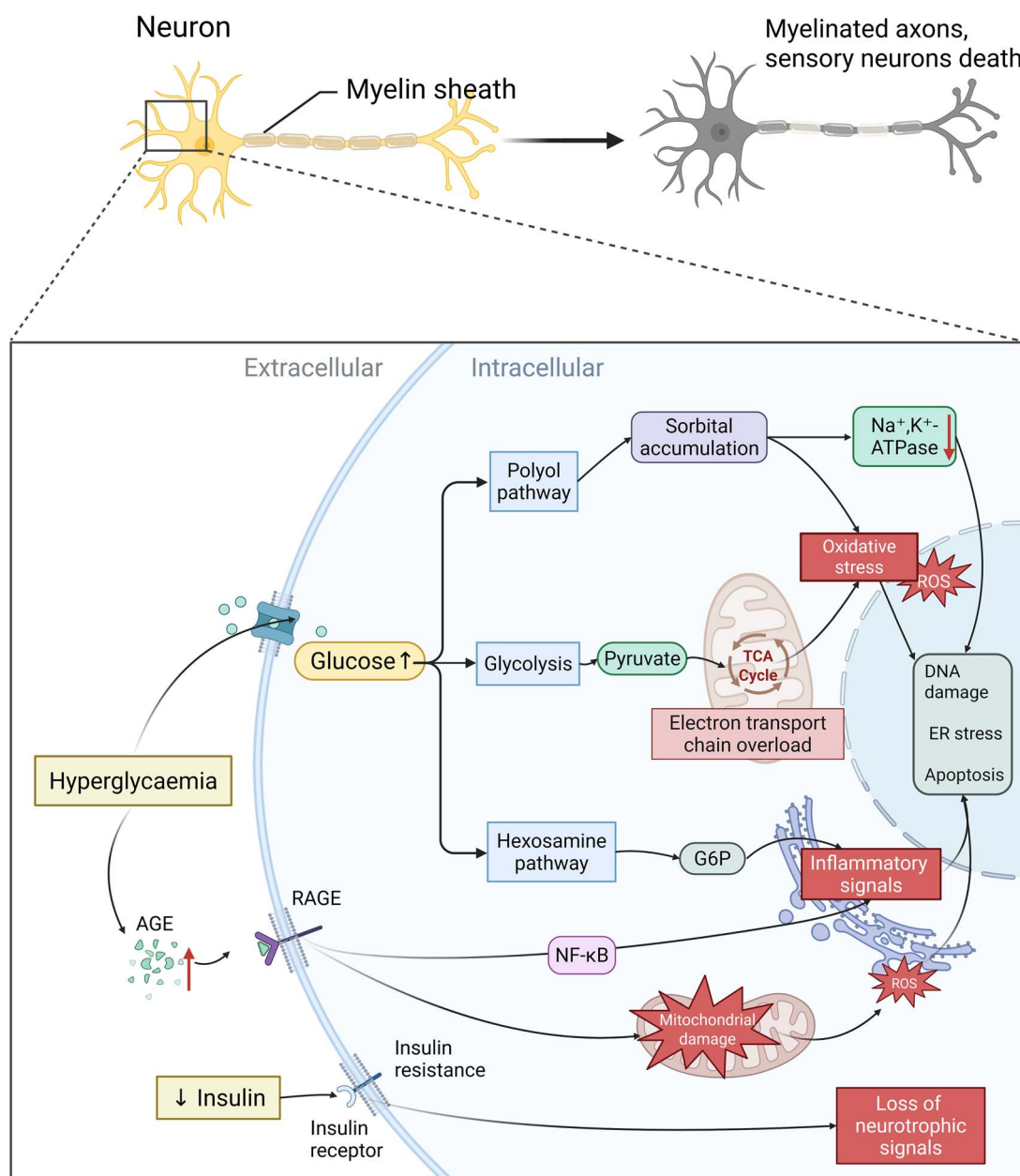


Figure 2. Pathogenesis of DPN. Hyperglycemia activates the hexosamine pathway. AGE binds to RAGE and triggers a signaling cascade that activates NF- κ B, leading to the transcription of inflammatory genes, mitochondrial damage, and DNA damage. Hyperglycemia causes sorbitol accumulation, reduced Na⁺-K⁺-ATPase activity, and mitochondrial dysfunction due to overload of glycolysis, the TCA cycle, and oxidative phosphorylation. These pathways result in neural signaling loss and cellular damage, contributing to DPN. TCA cycle tricarboxylic acid cycle, DPN diabetic peripheral neuropathy, NF- κ B nuclear factor kappa B

interventions is crucial for alleviating the symptoms of DPN [60, 61]. It is imperative for healthcare professionals to offer comprehensive care and education to patients with diabetes to reduce the detrimental effects of DPN on their quality of life and overall health outcomes [54, 62, 63]. Addressing oxidative stress is a key element in this holistic care approach (Figure 2).

Studies have shown that Schwann cell pyroptosis impairs peripheral nerve regeneration, a phenomenon particularly relevant in DPN. Rab32 exacerbates peripheral nerve injury-induced Schwann cell pyroptosis by reducing neurofibromin and increasing ROS production. Rab32 inhibition reduces Schwann cell pyroptosis and promotes nerve regeneration.

Therefore, targeting Rab32 is a promising strategy for mitigating oxidative stress and reducing high ROS levels, potentially alleviating DPN progression while promoting peripheral nerve regeneration and functional recovery [64].

Diabetic peripheral sensory neuropathy. Sensory and motor peripheral neuropathies are the most common neurological issues in patients with diabetes [65]. Within the umbrella of DPN, diabetic sensory neuropathy can lead to decreased sensations of pain, pressure, and temperature, along with proprioception problems [65–67]. Patients with diabetic neuropathy often experience symmetrical pain in their extremities, particularly in the distal areas, described as

a gloves-and-socks pattern. This change can reduce pain awareness and lead to a loss of protective sensation, resulting in unnoticed injuries. Oxidative stress plays a key role in the induction of nerve damage [54]. Under hyperglycemic conditions, abnormalities in the mitochondrial electron transport chain and activation of NADPH oxidase generate large amounts of ROS [68]. Additionally, the accumulation of polyols and the formation of AGEs promoted by high blood sugar levels can lead to metabolic and microvascular changes that impair nerve function [69, 70]. Unfortunately, oxidative stress-related nerve damage often progresses silently, causing early symptoms to go unnoticed until irreversible damage occurs. These oxidative changes make diabetic sensorimotor peripheral neuropathy a major risk factor for DFUs and Charcot arthritis, both of which can ultimately lead to lower-limb amputation [71].

Currently, no drugs have been specifically designed to treat DPN, including the sensory and motor aspects. Existing medications for preventing and managing this disease have limited efficacy and may cause side effects, posing a significant health-care challenge [54, 72]. Additionally, diabetic neuropathy can affect balance and gait, which is particularly concerning in older patients with diabetes, as it increases the risk of falls. Antioxidant strategies may help mitigate these effects [66].

Peripheral motor neuropathy. Under the DPN category, diabetic peripheral motor neuropathy (DPMN) primarily manifests as motor nerve damage, leading to muscle weakness, atrophy, and limb movement dysfunction. This condition often coexists with sensory and autonomic neuropathy. Clinical signs and symptoms of DPMN usually appear in advanced cases, with motor involvement being relatively rare. Severe DPMN may cause weakness of the ankle dorsiflexors, making it difficult for patients to stand [73]. According to Dyck *et al.*, these patients were classified as Type 2b [74].

Interestingly, although sensory symptoms and signs are more prominent during clinical examinations, nerve conduction studies have shown similar damage to both motor and sensory nerves [67]. Initially, sensory symptoms occur when the most distal portions of the sensory nerves in the toes begin to deteriorate. As neuropathy progresses and involves more proximal nerves, motor dysfunction may occur, resulting in foot muscle denervation [75].

This is primarily due to the excessive production of ROS under high-glucose conditions, leading to mitochondrial dysfunction and lipid peroxidation, which impair motor nerve conduction function [56]. As diabetic sensorimotor peripheral neuropathy progresses, foot muscle weakness and atrophy may become unnoticed, while oxidative stress drives the progressive deterioration of motor function [76]. Although interosseous bone atrophy may be present in the hand, symptoms of weakness are usually not apparent [53]. Motor dysfunction becomes more evident later in the disease [77, 78].

Autonomic neuropathy. Diabetic autonomic neuropathy (DAN) is an often underestimated complication of diabetes despite its significant impact on patient survival and quality of life [79, 80]. DAN can occur independently or in conjunction with other diabetes-related complications, affecting multiple organs throughout the body. Neurovascular dysfunction associated with DAN can lead to a range of clinical problems, including erectile dysfunction, dermatological issues, and vascular dysreflexia. Early signs of DAN can often be detected

through disruptions in microvascular blood flow in the skin, manifested by symptoms such as dry skin, decreased sweating, and skin cracks, which may allow harmful microorganisms to enter. Oxidative stress further exacerbates these microvascular changes, impairs blood flow, and compromises skin integrity. If left untreated, these initial changes can lead to more serious complications, such as ulcers, gangrene, and even amputation. Although specialized tests can assess neurovascular function, the diagnosis and management of DAN remain challenging due to a lack of standardization and limited clinical utility [81].

Sensory and structural abnormalities

Structural deformities, such as those caused by Charcot foot neuropathy and bone resorption, can increase pressure. Similarly, motor neuropathy can result in foot deformities and biomechanical abnormalities that significantly alter foot structure and function [82].

Other critical factors also contribute to foot ulcer development, including prolonged low pressure from tight shoes, which may lead to tissue necrosis, and high external pressure from sharp objects, which can cause direct mechanical damage [83, 84]. The combined effects of these factors underscore the complexity of DFU pathology [85, 86].

Antioxidant strategies for the management of diabetic foot ulcers

Oxidative stress is a key factor in wound formation and impaired healing in individuals with diabetes, as dysfunction in antioxidant defense mechanisms significantly prolongs the healing process [56]. A study on ROS in biological systems, first highlighted by Commoner *et al.* in 1954, demonstrated their harmful effects on cells by initiating oxidative processes [83]. ROS have been implicated in the development of various diseases, including neurodegenerative disorders [87], cardiovascular conditions [88], and diabetes. In individuals with diabetes, excessive ROS production overwhelms cellular antioxidant defenses, leading to cellular damage or death [89, 90]. This imbalance is particularly detrimental to DFUs, as persistent infection and inflammation frequently delay healing. ROS exacerbates these conditions, affecting multiple stages of the wound healing process, from the initial inflammatory phase to the later stages of tissue repair and remodeling [56, 91]. In DFUs, heightened oxidative stress, coupled with diminished antioxidant defenses, creates an environment in which wound healing is severely compromised. The accumulation of ROS not only damages cellular components but also disrupts signaling pathways essential for effective wound repair. This disruption leads to prolonged inflammation, impaired angiogenesis, and delayed re-epithelialization, all contributing to the chronic nature of wounds.

Maintaining a balance between ROS production and antioxidant defense is essential for effective wound healing in individuals with diabetes. Therapeutic strategies targeting oxidative stress, either by enhancing antioxidant defenses or reducing ROS production, could play a pivotal role in improving healing outcomes for patients with DFUs. Understanding the intricate relationship between oxidative stress and wound healing in diabetes is crucial for developing targeted interventions that mitigate the harmful effects of ROS and promote faster and more effective wound repair.

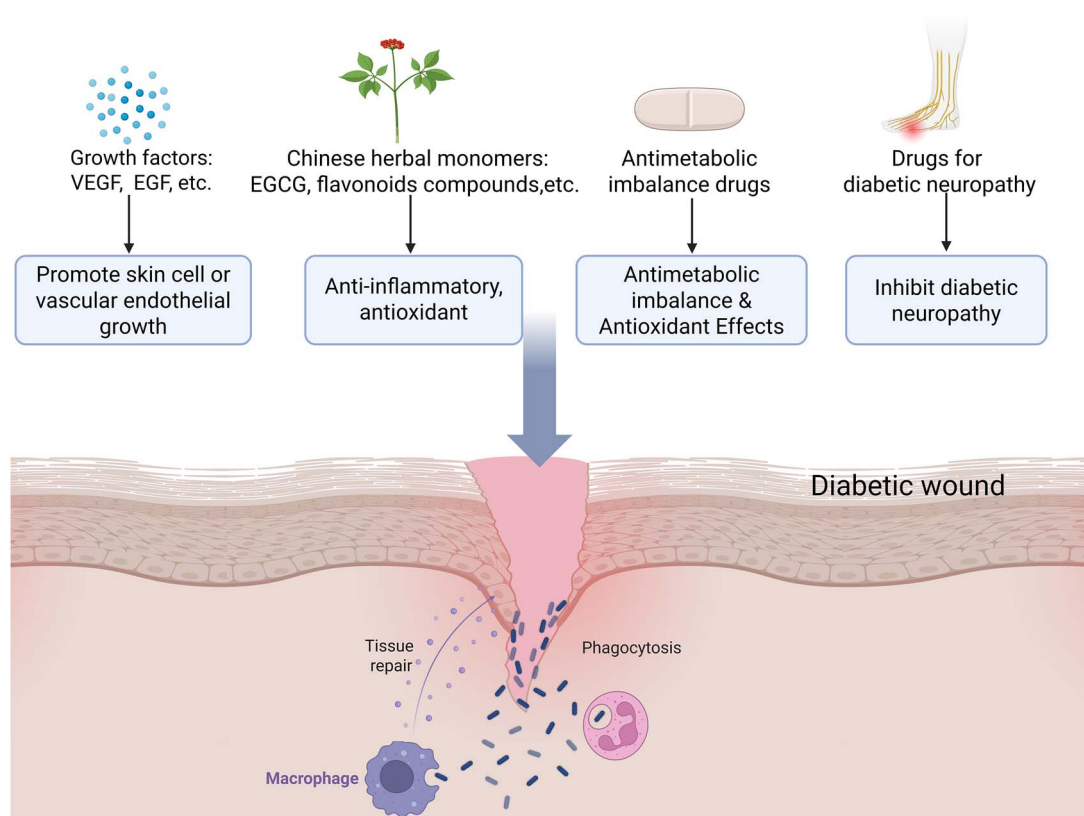


Figure 3. Examples of drugs that promote diabetic wound healing and the underlying mechanisms. Growth factors enhance angiogenesis and the formation of granulation tissue, which are essential for wound repair. TCM monomers are bioactive compounds derived from traditional Chinese medicinal herbs. They exhibit various pharmacological effects, such as anti-inflammatory, antioxidant, and antimicrobial activities, which contribute to wound healing. Anti-metabolism drugs aim to correct metabolic disturbances associated with diabetes, such as hyperglycemia and dyslipidemia, which can impair wound healing

Various components, including nanomaterials, small-molecule antioxidants, hydrogels, and TCM ingredients, have demonstrated the ability to stimulate multiple phases of the wound-healing process through antioxidant mechanisms [92]. Recent reviews have explored the advancements and current clinical strategies in this area, highlighting the potential of these components to enhance wound repair (Figure 3). The use of antioxidant-focused strategies in biomaterial development holds significant potential for enhancing wound healing and tissue repair, paving the way for more effective and innovative therapies for individuals with DFUs [93].

To systematically classify functional components and their therapeutic mechanisms, Table 1 delineates five major categories of antioxidant-based therapeutic interventions for diabetic wound healing. Each category is characterized by its unique mechanism of action and associated signaling pathways through which it imparts therapeutic benefits, including oxidative stress mitigation, inflammatory modulation, and tissue regeneration potentiation [94–117].

Modulating oxidative stress by small molecule antioxidants

Cell growth factors. Cell growth factors are crucial in regulating cellular interactions and coordinating the healing process during normal wound healing [118]. However, diabetic wounds exhibit an imbalance in this mechanism, leading to impaired angiogenesis and delayed healing [119]. Releasing growth factors from wounds is essential for accelerating

healing, underscoring their importance in tissue repair [120]. Recent studies have further explored the relationship between growth factors and reparative cells, highlighting their critical role in repair mechanisms [121].

Epidermal growth factor (EGF) is recognized as a prominent cytoprotective growth factor [122], and its protective effects are primarily mediated through agonistic stimulation of the phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway, which is activated by the phosphorylation of the EGF receptor [123]. Numerous *in vitro* and *in vivo* experimental studies have illustrated EGF's remarkable capacity to improve the survival rates of cells, tissues, and whole organisms when faced with potentially lethal challenges. These challenges include exposure to cytotoxic oxidants [124] and incidents of ischemia/reperfusion in parenchymal organs [125]. Overall, the administration of exogenous EGF has been shown to effectively diminish the production of malondialdehyde, mitigate cell and tissue death, and activate antioxidant defense mechanisms in the body. Furthermore, EGF has been widely explored in the context of DFUs, demonstrating significant benefits in reducing oxidative stress and enhancing repair processes associated with wound healing [126]. Specifically, when EGF is injected into the peri-wound area, it appears to have a systemic impact, potentially reverting the impaired redox state often observed in diabetes to a more normalized physiological condition. This shift is crucial, as it promotes the survival and proliferation of wound-related cells, ultimately leading to

Table 1. Strategies for exploring antioxidants for DFU treatment

Antioxidant strategies	Examples	Results	Mechanism/signaling pathway	References
Small molecule antioxidants	Cell growth factors (EGF, FGF-1)	Promote the survival and proliferation of wound-related cells	PI3K–Akt signaling pathway; Increase the levels of TGF- β and PCNA	[94, 123, 130]
	Alpha-lipoic acid	Scavenge free radicals and reduce oxidative damage	Reaction with oxygen free radicals	[95]
	Antioxidant vitamins	Antioxidant and neurotrophic	Release active hydrogen to combine with ROO or·OH	[96]
	Dipeptidyl peptidase IV inhibitors	Reduces oxidative stress and improves neurological function	Blocking the AGE-RAGE signaling pathway	[97]
Chinese medicinal components	Flavonoid hesperidin	Hasten angiogenesis	Increase VEGF-c, TGF- β , and Smad-2/3; Ang-1/Tie-2 signaling pathway	[98, 99]
	EGCG	Combat apoptosis	Nrf2/ARE pathway	[100, 149]
	Resveratrol, Quercetin	Faster ulcer healing	Decrease HSPs	[101–105, 155, 157]
	Ferulic acid	Inhibited lipid peroxidation, improved wound healing	Reduce MMP (2, 8, 9) and increase TIMP-1 and 2	[106, 107]
	Chlorogenic acid	Promote migration and proliferation, improve wound healing	Elevate the level of reduced glutathione	[108]
Nanomaterials	Honokiol	Inhibit high glucose-induced Schwann cell damage	AMPK/SIRT1/PGC-1 α pathway	[158]
	CeO ₂ /Y ₂ O ₃ /Silver-loaded zirconium phosphate NPs	Enhance the wound healing capabilities and scavenging properties	/	[109, 177]
	AuNPs	Enhance the wound healing capabilities and scavenging properties	Inhibiting lipid peroxidation and preventing the production of ROS	[185–187]
Hydrogels	PBNPs	Facilitating proper wound healing and neovascular restructuring	Scavenge ROS	[195, 196]
	PLGA-PEG-PLGA (copper MOF materials containing MH and curcumin	Stimulate the growth of cells, the development of new blood vessels, and the production of collagen	Scavenge ROS	[198–203]
	Pluronic F-127 hydrogels	Promote collagen deposition and re-epithelialization, reduce inflammation	/	[204–207]
	The drug-loaded ROS-scavenging hydrogel	Accelerate wound healing	Decrease ROS level and upregulate M2 phenotype macrophages	[110, 111]
Other	Propolis	Accelerate wound healing	Increase GSH/GSSG ratio and interleukin-10, decrease TNF- α	[112, 113]
	Deferoxamine	Promote neovascularization and regeneration	Increase the hypoxia-induced factor - 1 alpha activation	[114, 115]
	N-Acetyl cysteine	Accelerate wound healing	/	[116, 117]

DFUs diabetic foot ulcers, ROS reactive oxygen species, EGF epidermal growth factor, FGF fibroblast growth factor, EGCG epigallocatechin-3-gallate, TGF- β transforming growth factor β , PCNA proliferative nuclear antigen protein, VEGF vascular endothelial growth factor, GSH glutathione, ROO Peroxyl radical

improved granulation, contraction, and re-epithelialization of the wound. Consequently, the effects of EGF, when applied around the wound site, can be likened to a form of 'replacement therapy', compensating for deficiencies in the systemic biochemical environment of diabetic patients and fostering enhanced healing outcomes. Recent studies on wound healing emphasized the critical role of growth factors in promoting cell repair [127]. Among these, fibroblast growth factor (FGF) has emerged as a crucial factor [128]. In particular, FGF-1, also referred to as acidic FGF, has been recognized for its ability to promote the formation of new blood vessels, thereby improving the blood supply to wounds [129]. This accelerates granulation growth, aids tissue repair, and supports skin cells. Studies have shown that FGF-1 shields blood vessels from oxidative stress, both *in vivo* and *in vitro* [130]. The angiogenic effects of FGF-1 are believed to result from increased production of angiopoietin, which leads to increased blood vessel formation [130]. Additionally, FGF-1 has been found to increase the number of blood vessels and fibroblasts in ulcerated tissue while also increasing the levels of TGF- β and proliferative nuclear antigen protein (PCNA), ultimately enhancing the healing of diabetic ulcers. Positive outcomes of studies linking FGF-1 to diabetic wound healing highlight its potential as a therapeutic agent for diabetic ulcers [131]. VEGF can activate multiple signaling pathways, such as the PI3K/Akt signaling pathway, to promote cell survival and enhance cellular antioxidant capacity. Additionally, VEGF indirectly activates the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, which is crucial for the cellular antioxidant response. Nrf2 translocates to the nucleus and binds to antioxidant response elements in DNA, promoting the transcription of antioxidant enzymes. This process enhances the ability of the cells to neutralize ROS and resist oxidative damage.

Research has shown a strong connection between growth factors involved in cell growth and wound healing in diabetes, demonstrating their effectiveness in combating oxidative stress in DFUs [120]. Although these growth factors have significant potential, their use is limited. To fully harness their healing potential for DFU treatment, optimizing transportation or delivery methods is crucial for practical application [132].

Alpha-lipoic acid. ALA is a potent and approved antioxidant drug for clinical use [67]. It has demonstrated significant efficacy in treating diabetes-related complications, particularly DPN and DFUs, and has been extensively evaluated in patients with DPN. The results indicate that alpha-lipoic acid effectively alleviates neuropathy symptoms in patients with DPN, including numbness, burning sensations, tingling, touch pressure sensitivity, and impaired ankle reflexes, and is highly safe and well tolerated [133]. Its primary mechanisms of action involve reducing the production of AGEs, preventing blood vessel and nerve damage associated with diabetes, scavenging free radicals, mitigating oxidative damage, and restoring redox balance. A randomized controlled trial demonstrated that oral administration of α -lipoic acid (600 mg/d) significantly improved neuropathy symptoms, including numbness, burning, tingling, touch pressure sensitivity, and impaired ankle reflexes after 4 years, confirming its high safety profile. Additionally, a meta-analysis indicated that intravenous administration of alpha-lipoic acid significantly enhanced short-term symptomatic relief

in peripheral diabetic neuropathy, highlighting its clinical relevance. Alpha-lipoic acid also protects vascular endothelial function by increasing nerve blood flow, enhancing nerve conduction velocity, boosting Na⁺-K⁺-ATPase activity, inhibiting lipid peroxidation, and exerting anti-inflammatory effects. In patients with DPN, alpha-lipoic acid administration significantly improves nerve conduction velocity and neurological function [134].

Antioxidant vitamins. B vitamins, including B6, B12, and nicotinamide, exhibit antioxidant and neurotrophic properties. Supplementation with these vitamins may mitigate oxidative stress and enhance neurological function in patients with DPN. A Phase III trial examining the effect of vitamin C on the healing of diabetic foot wounds indicated that a platelet-rich plasma fibrin glue dressing, when combined with oral vitamins E and C, facilitated wound healing and diminished oxidation [135]. Stress has been shown to impair wound healing in patients with foot ulcers. Additionally, vitamin E can potentially alleviate symptoms of pinprick pain in individuals with DPN. Research has demonstrated that tocotrienols, a form of vitamin E, can modulate neuropathways and alleviate neuropathological symptoms through their antioxidant and anti-inflammatory effects [136].

Dipeptidyl peptidase IV inhibitor. The hypoglycemic drug dipeptidyl peptidase IV inhibitor (DPP-4i) also exhibits potent antioxidant properties. Among these agents, texagliptin has been shown to alleviate nerve pain by increasing GSH levels [137]. In a streptozotocin-induced rat model of DPN, the novel DPP-4i PKF275-055 prevented the progression of DPN when administered at a low dose (3 mg/kg for 4 weeks) and a high dose of (10 mg/kg for 5 weeks), potentially improving anabolic function. Furthermore, DPP-4i treatment may enhance wound healing in patients with DFUs by reducing oxidative stress [138].

In an experimental study in rats, dexmedetomidine effectively improved oxidative stress associated with DPN. By observing several indicators of oxidative stress, researchers found that dexmedetomidine reversed the reduction in motor nerve conduction velocity, mechanical withdrawal threshold, and thermal withdrawal latency induced by DPN. This treatment reduced oxidative stress, mitochondrial damage, and apoptosis. This specific mechanism involves dexmedetomidine's regulation of the SIRT2/S1PR1 axis by downregulating miR-34a, thereby alleviating DPN-related oxidative stress and mitochondrial dysfunction. This suggests that dexmedetomidine plays a protective role in peripheral neuropathy and has promising prospects for the treatment of DPN [139]. Another experimental study in rats found that inosine has a therapeutic effect on DPN. Rats were categorized into groups and treated accordingly. Studies have found that inosine can lower blood sugar and improve sciatic nerve function by restoring tissue structure, enhancing myelination, regulating conduction velocity, and maintaining behavioral responses. The mechanism of action involves regulating the GLO1/AGEs/RAGE/NF- κ B/Nrf2 and TGF- β /PKC/TRPV1/SP signaling pathways. Specifically, inosine increases GLO1, reduces the AGE/RAGE axis and oxidative stress, and downregulates NF- κ B p65. Its phosphorylated form enhances the expression of Nrf2 and heme oxygenase-1 (HO-1), inhibits the expression of PKC and TRPV1, and relieves pain. Research has shown that inosine has potential

therapeutic effects on hyperglycemia-induced DPN, improves multiple indicators, and has promising prospects for treating diabetic foot [140].

Antimicrobial therapy. DFUs are highly susceptible to bacterial infections due to impaired immune function, poor blood circulation, and high blood sugar levels in patients with diabetes, which compromise the body's ability to fight infections. Timely and appropriate antibiotic therapy is essential to control infection, promote healing, and prevent complications, such as sepsis or amputation [141]. Antimicrobial therapy plays a key role in treating DFUs. For example, mupirocin is a topical antibiotic that inhibits bacterial protein synthesis, effectively reduces the bacterial load, and promotes wound healing. It is particularly useful against methicillin-resistant *Staphylococcus aureus* (MRSA), a common pathogen in DFUs [142]. Another example is linezolid, an oral or intravenous antibiotic that targets Gram-positive bacteria by inhibiting bacterial ribosomal function. Linezolid is effective against various bacteria, including MRSA and vancomycin-resistant enterococci, making it a valuable option for the treatment of severe DFUs [143]. In conclusion, antibiotics are an essential part of managing diabetic foot infections, playing a pivotal role in controlling bacterial growth, promoting wound healing, and preventing complications like sepsis and amputation.

Limitation of small molecule drugs. Small-molecule drugs, although effective in certain scenarios, have significant limitations. One challenge is their susceptibility to degradation within the body, which results in a short half-life and makes it difficult to sustain an effective concentration at the wound site. Additionally, their delivery efficiency is often suboptimal. For instance, when applied topically, small-molecule drugs are easily degraded by proteases, leading to significantly reduced bioavailability [144]. Targeting specificity is another limitation in this context. For example, certain small-molecule drugs, such as growth factors, exhibit broad-spectrum effects but cannot precisely target and modulate specific oxidative stress pathways. This limitation can hinder efforts to mitigate oxidative stress in chronic wounds effectively. For instance, ALA demonstrates limited efficacy in addressing the complex oxidative stress associated with DFUs. Similarly, DPP-4i regulates oxidative stress by inhibiting GLP-1 degradation. However, in advanced DFUs or severe infections, these inhibitors' therapeutic effects may be minimal [145].

Common limitations shared by most small-molecule drugs include insufficient delivery systems. Most small-molecule drugs lack effective delivery carriers, resulting in inadequate drug concentrations or uneven distribution within wound tissues. Complex multipathway regulation: the pathological mechanisms of DFUs are multifactorial, encompassing inflammation, infection, and angiogenic disorders. A single small-molecule drug targeting oxidative stress is often insufficient to address these interconnected factors comprehensively. Challenges in the chronic wound environment: prolonged oxidative stress and an inflammatory microenvironment in chronic wounds can reduce the sensitivity of small-molecule drugs, making them less effective than their performance in acute wounds. Drug tolerance and toxicity: Long-term use of small-molecule drugs may lead to drug tolerance or cumulative toxicity, posing challenges for treatment safety and efficacy. These limitations highlight the need for innovative approaches to enhance the therapeutic potential of

small-molecule drugs in treating DFUs, particularly through improved delivery systems and combination therapies.

Modulating oxidative stress by Chinese medicinal components

One of the core elements of TCM is Chinese herbal medicine, which has been practiced for more than 3000 years as part of a holistic approach to health. This practice combines herbs with acupuncture, dietary therapy, bodywork, and movement techniques to manage and prevent various health issues. Chinese herbal medicine promotes injury recovery by cleansing the body, increasing blood flow, and alleviating stagnation [146].

The flavonoid hesperidin, found in tangerine peel, is a key component of TCM. Research suggests that hesperidin can reduce oxidative stress damage associated with diabetes, elevate the mRNA expression levels of VEGF-c, TGF- β , and Smad2/3 in diabetic wounds, and activate the angiotensin-1/tyrosine kinase receptor 2 (Ang-1/Tie-2) signaling pathway, thereby promoting wound healing [147]. Collectively, these mechanisms aid in hastening angiogenesis and facilitating the healing of chronic DFUs.

In the context of DFUs and their response to oxidative stress, the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway is crucial for maintaining intracellular redox balance. Nrf2 regulates the expression of antioxidant enzymes such as GSH and HO-1, which are vital for neutralizing ROS and mitigating oxidative stress. Nrf2 activation has been shown to modulate inflammatory responses, reduce oxidative injury, and promote healing in diabetic wounds [148].

Recent research has focused on natural compounds that can activate Nrf2, with green tea emerging as a significant source of catechins, particularly (–)-epigallocatechin-3-gallate (EGCG). EGCG is a potent Nrf2 activator that combats oxidative stress, inflammation, and diabetes-induced apoptosis, highlighting its potential for treating persistent diabetic wounds [149].

Additionally, Huangbai liniment (HB), a traditional medication used for wound treatment, has been shown to accelerate wound healing and enhance ECM production in diabetic rats. HB activates Nrf2 and its downstream antioxidant genes, thereby reducing oxidative damage and preventing apoptosis. *In vitro* studies have demonstrated that HB stimulates the proliferation of human immortalized keratinocytes under high-glucose conditions while simultaneously reducing oxidative stress. These findings suggest that HB and other Nrf2 activators play significant roles in managing and treating chronic diabetic wounds, offering new avenues for therapeutic intervention [150].

Other natural compounds (such as resveratrol and quercetin) or specific HSP inducers can increase the expression of HSP through different signaling pathways [151]. HSPs are a group of cellular proteins that respond to various stressors such as heat shock, cold, ultraviolet rays, and wound healing [152]. These proteins are essential for promoting wound healing and maintaining the protein balance in dermal fibroblasts [153]. One type of HSP, HSP27, is a small heat shock protein that plays roles in cell differentiation, development, heat resistance, and apoptosis inhibition [154]. Patients with cancer, muscle and neurodegenerative diseases, diabetes, and DPN have increased HSP27. Another essential protein, HSP70, protects cells from oxidative and heat stresses [155]. Patients

with diabetes have elevated serum levels of HSP70, which protects against oxidative conditions. High levels of HSP47 have been observed in DFUs, whereas increased HSP70 levels have been associated with faster ulcer healing [156]. Elevated HSP47 levels are associated with delayed gastric ulcer healing. Targeting the expression of these heat shock proteins may improve the healing process of DFUs [157].

Previously, we reported that pyroptosis is the primary mode of Schwann cell death in DPN. Honokiol reduces high glucose (HG)-induced oxidative stress, ferroptosis, and mitochondrial dysfunction in Schwann cells. The results show that honokiol restores HG-induced inhibition of the AMPK/SIRT1/PGC-1 α axis and alters downstream gene expression profiles. Furthermore, silencing SIRT1 via siRNA delivery significantly reduces HG-induced changes in gene expression profiles in HG-treated Schwann cells. Honokiol significantly attenuates DPN by improving sciatic nerve conduction velocity and increasing thermal and mechanical sensitivity in streptozotocin-induced diabetic rats. Collectively, these results indicate that honokiol attenuates HG-induced Schwann cell damage and peripheral nerve dysfunction, suggesting a potential strategy for the treatment of DPN [158].

Although TCM monomers targeting oxidative stress show promise for the treatment of DFUs, some limitations remain. A major limitation is the poor bioavailability and stability of these monomers, which reduce their therapeutic efficacy. Furthermore, the complex pathophysiology of DFUs often requires a multitarget approach, and a single monomer may not be sufficient to address all underlying mechanisms. Variations in the quality and concentration of active ingredients in TCM preparations can also lead to inconsistent clinical results. Additionally, the lack of standardized dosing regimens and potential interactions with other drugs pose challenges to their integration into conventional treatment protocols.

Studies have shown that combining the five main monomer components of the Wuziyanzong Pill helps prevent neural tube defects by reducing apoptosis and oxidative stress. This combination approach leverages the multi-target nature of these compounds, providing a broader spectrum of activities that can overcome the limitations of single-agent therapies. Research indicates that this combination can produce additive or synergistic effects, enhancing the antioxidant, anti-apoptotic, and anti-inflammatory activities. Although no reports currently exist on combining Chinese medicine monomers to treat diabetic foot, integrating them with other therapeutic drugs or using Chinese medicine compounds that simultaneously target multiple pathways may enhance their efficacy. Future studies could explore this approach as a potential treatment option for diabetic foot, thereby offering a more comprehensive treatment strategy [159]. Additionally, chemical modifications to TCM monomers to enhance their specificity may improve their efficacy [160].

The application of nanotechnologies on the management of DFUs via modulating oxidative stress

Recently, nanoengineered biomaterials have played a critical role in improving DFU treatment [161]. Specifically, nanoparticles (NPs) have been found to act as scavengers for free radicals, aiding in the healing process of DFUs [162]. Nanoengineered biomaterials have revolutionized DFU treatment, providing more efficient healing methods [163]. Ongoing research on nanotechnology for diabetes treatment has highlighted the importance of NPs in managing various

aspects of the disease [164, 165]. The discovery of NPs as free radical scavengers presents new possibilities for enhancing DFU healing [166] (Figure 4).

Metal nanoparticles. Metal nanoparticles have garnered significant attention in biomedical research because of their capacity to modulate oxidative stress, a critical factor in various pathological conditions, including chronic wounds and diabetic ulcers. By scavenging ROS and catalyzing redox reactions, these nanoparticles help restore oxidative balance, thereby promoting tissue repair and preventing further damage. Among them, cerium oxide (CeO₂) stands out due to its unique redox properties and potent antioxidant capabilities.

CeO₂ NPs have gained attention due to their potential to treat DFUs by functioning as free radical scavengers [167]. These NPs are characterized by their uniform size, single-crystal structure, limited twin boundaries, and larger-than-normal lattice parameters [168, 169]. Among these NPs, Ce atoms display two different oxidation states, +4 and +3, leading to the formation of oxygen vacancies [170]. The reduction of Ce⁴⁺ to Ce³⁺ through the loss of oxygen contributes to the formation of oxygen vacancies, enhancing the wound-healing and scavenging properties of CeO₂ NPs [170]. The dual oxidation states of Ce atoms within CeO₂ NPs are crucial for their potential effectiveness in DFU healing [171]. This unique characteristic enables the creation of oxygen vacancies, which have been linked to improved wound-healing properties and the ability to scavenge harmful free radicals. Through the reduction of Ce⁴⁺ to Ce³⁺ and the subsequent formation of oxygen vacancies, CeO₂ NPs have shown promise in promoting the healing of DFUs [172, 173].

Yttrium oxide (Y₂O₃) has been identified as a promising candidate for DFUs due to its high free energy of oxides formation from elemental yttrium, which distinguishes it from other metal oxides [174]. Its minimal stoichiometric changes at room temperature and pressure further enhance its appeal for potential medical applications. Studies have shown that Y₂O₃ NPs are generally safe for neutrophils and macrophages, demonstrating good biocompatibility [175, 176]. Furthermore, the effectiveness of cerium oxide and yttrium oxide NPs in protecting cells from oxidative stress-induced cell death is critically influenced by the nanoparticle structure, underscoring their potential in DFU treatment [177]. These findings suggest that further research on Y₂O₃ NPs for DFU therapy could lead to promising advancements in medical science [176].

The potential scavenging capabilities of NPs derived from various metal oxides, such as aluminum oxide (Al₂O₃) and silver nitrate, warrant consideration for DFU treatment [178, 179]. Silver nitrate, a renowned antimicrobial agent, has been the subject of extensive research because of its proven efficacy in combating a broad spectrum of pathogens during chronic wound treatment [180, 181]. In addition to silver nitrate, novel formulations such as silver-loaded zirconium phosphate NPs have demonstrated substantial promise in diabetic wound care [182–184]. Moreover, gold NPs (AuNPs) have attracted significant attention for their medical applications, particularly in restoring antioxidant balance [185, 186]. These gold NPs inhibit lipid peroxidation and reduce ROS [187], thereby playing a crucial role in maintaining cellular health. Given these properties, NPs from various metal oxides, including aluminum oxide, silver nitrate, and gold, hold considerable potential for effective DFU treatment.

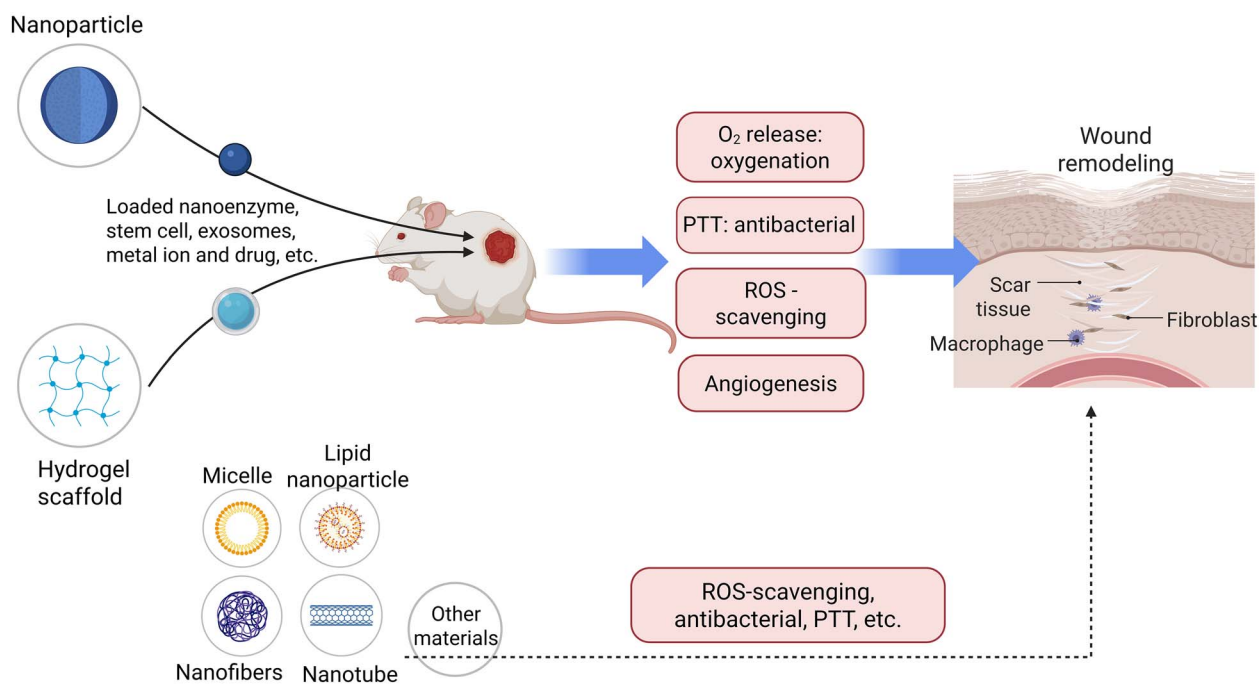


Figure 4. Nanotechnology for the treatment of diabetic wounds. Encapsulating antibiotics, anti-inflammatory drugs, and antioxidants in nanoparticles enables controlled drug release, enhancing drug stability and bioavailability. For example, poly (lactic-co-glycolic acid) (PLGA) nanoparticles can be utilized for the sustained release of drugs, prolonging their therapeutic action at the wound site. Nanohydrogels exhibit excellent biocompatibility and moisture retention properties, providing a moist healing environment for wounds. They can also load and release various therapeutic molecules, such as nanozymes, stem cells, anti-inflammatory drugs, and growth factors. Other nanomaterials, including nanofibers, nanotubes, exosomes, and lipid nanoparticles, effectively treat DFUs by encapsulating drugs or leveraging their high surface area and porosity for drug loading and release. *PTT* photothermal therapy

In conclusion, the application of nanoengineered biomaterials, particularly NPs, has dramatically improved the management and healing of DFUs [188]. Research on nanotechnology for diabetes treatment is a significant area of focus and has revealed the potential of NPs as free radical scavengers [189]. This advancement holds promise for enhancing the overall outcome of DFU treatment.

Hydrogels. The current focus of scientific investigations is the development of materials with scavenging abilities to shield the wound bed from ROS-induced damage [190]. Hydrogels play a crucial role in regulating oxidative stress by maintaining a moist environment and scavenging ROS, which facilitate tissue repair. Additionally, they serve as a delivery platform for nanoparticles, enabling their controlled release and enhanced stability, thereby improving the efficacy of treatments aimed at mitigating oxidative stress. Hydrogels, as polymeric materials in a 3D form, show promise for designing DFU dressings by establishing a moist environment that promotes cell growth and tissue renewal, ultimately minimizing scarring [191].

A recent study by Xu *et al.* described the creation of hydrogels composed of poly (D, L-lactide)-PEG-poly (D, L-lactide) (PLGA-PEG-PLGA) to encapsulate and release Prussian blue NPs (PBNPs) [192]. These NPs mimic the ROS-scavenging capabilities of natural antioxidant enzymes, such as peroxidase, catalase (CAT), and superoxide dismutase (SOD) [193]. The hydrogel's responsiveness to temperature enables gelation at body temperature [194]. Experiments conducted in a diabetic mouse wound model confirmed the ability of PBNPs to scavenge ROS, as demonstrated by dihydroethidium staining [195]. Consequently, chronic inflammation decreased,

observed, facilitating proper wound healing and neovascular restructuring compared to the control treatment, which lacked PBNPs [196].

Yang *et al.* aimed to create a versatile hydrogel system that could regulate blood sugar levels and oxidative stress in diabetic wounds [197]. They prepared copper metal-organic framework (MOF) materials containing metformin hydrochloride (MH) and curcumin using solvothermal techniques [198]. Curcumin, recognized for its ability to scavenge ROS, was combined with MH, a medication used to lower blood sugar levels [199]. The resulting MOF exhibited a drug retention rate of approximately 65% and was incorporated in a PLGA-PEG-PLGA heat-sensitive hydrogel for gradual drug release [200]. The effectiveness of the hydrogel was assessed in a type 1 diabetes wound model, which demonstrated a notable decrease in blood sugar levels throughout the treatment period [201]. The antioxidant capabilities of the hydrogels were confirmed using chemiluminescence analysis [202]. Examination of the wound indicated that the mixed dressing stimulated cell growth, new blood vessel formation, and collagen production, ultimately resulting in the closure of more than 90% of the wound after 20 days [203].

Pluronics, also known as poloxamers, are triblock copolymers consisting of polyethylene oxide/polypropylene oxide/polyethylene oxide. These polymers are FDA-approved for medical use and are considered safe and nontoxic. Pluronics, particularly Pluronic F-127 hydrogels, have gained attention in the biomedical field because of their ability to act as synthetic platforms for delivering drugs and cells in gel form at body temperature [204, 205]. Researchers such as Jiao

et al. have explored the use of a 20% w/v Pluronic F-127 hydrogel encapsulating Wharton's jelly mesenchymal stem cells (WJMSCs) for treating type 2 diabetic wounds [204]. This study enriched a hydrogel precursor with sodium ascorbyl phosphate to improve the viability of WJMSCs before encapsulation [206]. Research has shown that hydrogel dressings significantly enhance the healing process in diabetic wounds by promoting collagen deposition, supporting re-epithelialization, and reducing inflammation 14 days after transplantation [207]. Additionally, the successful engraftment of WJMSCs into wounds demonstrated the regenerative and immunomodulatory potential of the hydrogel system for treating DFUs. Overall, this study highlights the promising role of Pluronic F-127 hydrogels in enhancing wound healing, particularly in patients with diabetes [205].

Altogether, these hydrogel-based frameworks exhibit mechanical characteristics similar to those of soft tissues and can be chemically or physically modified to serve as carriers of bioactive substances that aid in effective wound recovery [208]. DFU prediction has significant potential for future research.

Limitations of Nanomedicines: Metal nanoparticles, hydrogels, and other nanomaterials have shown promise in treating diabetic wounds. However, some challenges exist: an insufficient concentration of drug-loaded nanocarriers in deep wounds may result in inadequate antioxidant effects [209, 210]. In antioxidant treatments, nanomaterials may disrupt the body's normal redox balance and inhibit essential signaling pathways. For example, Au nanoparticles can cause excessive activation of macrophages after prolonged retention, which may negatively affect wound healing. The long-term presence of metal ions in wounds can induce chronic immune responses or interfere with local tissue repair [211, 212].

In addition to the inherent limitations of these materials, achieving multiple functions, such as antioxidant, anti-inflammatory, and antibacterial effects, requires a complex nanomaterial design. This complexity increases production costs and process difficulties, therefore limiting clinical translation. Furthermore, some nanomedicines require external stimulation (such as light or lasers); however, their practical application may be constrained by wound depth or environmental conditions [213, 214]. For instance, nanoparticles loaded with photothermal therapeutic agents (such as IR820 or indocyanine green) have limited effectiveness in deep diabetic ulcer tissue because of insufficient light penetration [215].

Nanomaterials exhibit potent antibacterial effects via diverse and highly flexible mechanisms. Some antibacterial nanomedicines function through metal ions, such as silver nanoparticles (AgNPs), which are known for their broad-spectrum antibacterial activity. AgNPs inhibit bacterial growth by interacting with bacterial membranes, inducing oxidative stress and interfering with bacterial DNA. They reduce the bacterial load and promote tissue regeneration in diabetic wounds [216].

Nanomaterials can serve as efficient drug delivery carriers, and some nanomedicines contain antibacterial ingredients that enhance their stability and bioavailability. For example, chitosan nanoparticles can be loaded with antibiotics (such as gentamicin or ciprofloxacin) to provide prolonged local antibacterial effects through a sustained-release mechanism, preventing rapid drug degradation [217]. Polymeric

nanomaterials or liposomes can also effectively deliver drugs to infection sites, enhance their antibacterial effects, and reduce systemic toxicity. For instance, TCM monomers, such as curcumin and berberine, can be loaded into nanocarriers to form composite materials, enhancing their antibacterial properties and prolonging their duration of action [214]. These hydrogels provide a moist environment for wounds while continuously releasing the active ingredients of TCM, significantly improving their antibacterial and anti-inflammatory effects [218]. Nanomedicines that utilize photothermal effects for antibacterial activity include nanomaterials with photothermal properties (such as AuNPs and graphene oxide). These materials generate high local temperatures under laser irradiation, killing bacteria through thermal effects while avoiding damage to healthy tissues. This method is particularly suitable for the treatment of wounds infected with drug-resistant bacteria [219].

The clinical adoption of nanoparticle-based systems faces two challenges: biodegradability profiles and scalable manufacturing. While nanoparticles demonstrate variable degradation kinetics across material classes, certain synthetic polymers exhibit prolonged tissue retention with potential immunogenic consequences, necessitating a comprehensive toxicological evaluation of the degradation byproducts [220]. Compounding these biocompatibility concerns, physiological clearance mechanisms (e.g. renal filtration and hepatic metabolism) are often insufficient for nanosized structures, leading to systemic biodistribution patterns that require rigorous long-term safety assessments [221]. Moreover, transitioning from laboratory prototypes to commercial-scale production presents significant technical barriers, particularly in achieving batch-to-batch uniformity for multifunctional nanoparticles that require precision surface engineering [221]. The regulatory landscape further complicates clinical translation, as current guidelines lack standardized methodologies for evaluating the complex safety-efficacy balance inherent in nanotherapeutics, resulting in prolonged approval timelines that hinder market accessibility [222].

Future studies should focus on several key aspects to address these limitations. First, regarding engineered biodegradability, developing stimuli-responsive nanomaterials, such as those triggered by pH or enzymes, for controlled breakdown and safe metabolite excretion is crucial. Second, for cost-effective manufacturing, optimizing synthesis methods, such as microfluidic systems, or scalable approaches, such as bacterial expression systems (e.g. *Escherichia coli*-produced ferritin nanoparticles), can improve batch consistency and reduce production costs [223]. Third, regulatory collaboration is essential for establishing interdisciplinary frameworks that streamline the preclinical-to-clinical transition, including the development of harmonized guidelines for nanoparticle characterization and toxicity testing. Fourth, in biodegradable material design, developing stimuli-responsive nanocarriers, such as pH- or enzyme-sensitive polymers, can ensure controlled degradation and minimize off-target retention. In addition, conducting long-term toxicity assessments and establishing harmonized regulatory frameworks as part of translational studies can accelerate clinical translation. Finally, combination strategies that integrate nanotherapies with existing treatments, such as antibacterial agents or growth factors, should be explored to enhance synergistic effects [224].

Conclusions

This review discusses the application of the antioxidant modulation theory in the treatment of DFUs, emphasizing its critical role in enhancing wound healing and mitigating oxidative stress. By addressing the oxidative mechanisms that drive chronic wound formation, antioxidant strategies offer a promising avenue for improving diabetic ulcer care. However, the current body of research has certain limitations, including variability in the effectiveness of these treatments among different patients. Although preclinical and early clinical studies have shown promising results, further research is required to evaluate the efficacy of these novel antioxidants in real-world medical settings. By improving these strategies, the antioxidant modulation theory has the potential to revolutionize diabetic wound management, leading to more effective and personalized treatments that significantly improve patient outcomes. Future research should focus on developing nanoparticles with multifunctional properties that can simultaneously deliver therapeutic agents such as growth factors, antibiotics, anti-inflammatory drugs, and antioxidants. These nanocarriers enable controlled, sustained release, target specific pathways, enhance wound healing, and reduce side effects. Future studies should prioritize tailoring treatments for individual patients and rigorously evaluate the performance of emerging antioxidant therapies in clinical practice.

Acknowledgements

Figures were created with [BioRender.com](https://www.bio-render.com/).

Author contributions

Runze Wang (Conceptualization [equal]), Bowen Li (Conceptualization [equal]), Mengchao Dong (Conceptualization [equal]), Huili Zhu (Conceptualization [equal], Supervision [equal], Validation [equal]), Ping Jin (Conceptualization [equal], Project administration [equal]), and Yingying Zou (Conceptualization [equal], Project administration [equal], Supervision [equal]).

Conflict of interest

The authors declare no conflict of interest.

Funding

This work was partly supported by the National Natural Science Foundation of China (grant numbers 32060184, 81760149, and 82303506), Joint Special Funds for the Department of Science and Technology of Yunnan Province-Kunming Medical University (grant number 202401AY070001-029), the Scientific and Technological Innovation Team of Kunming Medical University (grant number CXTD202101), Yunnan Fundamental Research Projects (grant number 202401CF070184), Achievement Transformation Funding of Frontiers Medical Center, Tianfu Jincheng Laboratory (grant number 2025ZH048), First-Class Discipline Team of Kunming Medical University (2024XKT DTS11) and Yunnan Revitalization Talent Support Program.

Data availability

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Declarations

The authors declare that their participation in writing this review and its publication are voluntary.

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