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(REVIEW ARTICLE)

Diabetic wounds: Pathophysiology, complications and advances from conventional to modern therapies

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Abstract

Diabetic wounds, particularly foot ulcers, represent one of the most severe complications of diabetes mellitus, contributing to high morbidity, prolonged hospitalization and an increased risk of lower-limb amputation. Their management places a substantial economic burden on healthcare systems worldwide while severely impairing patients' quality of life. Conventional therapies such as glycemic control, debridement, infection management and surgical interventions remain the cornerstone of care but are often inadequate due to persistent oxidative stress, impaired angiogenesis, neuropathy and immune dysfunction. These pathological factors delay granulation tissue formation, collagen deposition and epithelialization, resulting in chronic, non-healing wounds with a high recurrence rate. In recent years, nutraceuticals have emerged as promising adjuncts to conventional therapy. Bioactive compounds such as vitamins C and E, zinc, copper, magnesium, curcumin, resveratrol, omega-3 fatty acids, probiotics and herbal extracts demonstrate diverse therapeutic properties, including antioxidant activity, modulation of inflammatory pathways, promotion of angiogenesis and enhancement of tissue remodeling. Advances in delivery systems, particularly nanoparticles and hydrogels, have further improved their bioavailability and clinical potential. Although preclinical findings are encouraging, clinical validation through well-designed randomized controlled trials remains limited. This review provides a comprehensive overview of the pathophysiology, risk factors and complications of diabetic wounds, outlines conventional therapeutic approaches and emphasizes the emerging role of nutraceuticals. By integrating nutraceuticals with standard care, future strategies may enable more effective, safe and cost-efficient management of diabetic wounds.

Keywords: Diabetic wounds; Foot ulcers; Nutraceuticals; Oxidative stress; Angiogenesis; Wound healing

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action or both. Its global prevalence has reached alarming proportions, with more than 589 million adults currently affected and projections indicating a rise to 853 million by 2050 [1]. Among its numerous

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complications, diabetic foot ulcers and chronic wounds represent a leading cause of morbidity, hospitalization and non-traumatic lower-limb amputations [2,3]. Approximately 19–34% of diabetic patients will develop a foot ulcer during their lifetime, with recurrence rates exceeding 40% within the first year after healing [4,5].

The burden of diabetic wounds extends far beyond clinical outcomes, encompassing significant public health and economic consequences. The management of diabetic foot ulcers accounts for nearly one-third of total diabetes-related healthcare expenditure in many countries, further compounded by reduced patient productivity, diminished quality of life and elevated mortality rates [6,7]. Conventional treatment strategies including surgical debridement, antibiotic therapy, glycemic control and vascular interventions have improved outcomes; however, complete healing remains suboptimal and recurrence is common [8,9]. These limitations underscore the urgent need for adjunctive therapies that directly target the underlying pathophysiological mechanisms of impaired wound healing.

Delayed healing in diabetic wounds results from the convergence of multiple pathological processes, including hyperglycemia-induced oxidative stress, chronic low-grade inflammation, impaired angiogenesis, neuropathy and peripheral arterial disease [10,11]. Collectively, these factors disrupt granulation tissue formation, collagen deposition and epithelialization, thereby prolonging wound closure [12]. Although essential, conventional therapies alone often fail to sufficiently address these cellular and molecular dysfunctions.

In this context, nutraceuticals—bioactive compounds derived from dietary sources with health-promoting properties—are increasingly recognized for their therapeutic potential in diabetic wound management. Compounds such as curcumin, resveratrol, omega-3 fatty acids, flavonoids and vitamins C and E have been shown to mitigate oxidative stress, modulate pro-inflammatory cytokines, stimulate angiogenesis and enhance extracellular matrix remodeling in both experimental and limited clinical studies [13–15]. By addressing fundamental molecular impairments, nutraceuticals represent promising complementary agents when used alongside conventional therapies.

Recent advances in nanotechnology and novel delivery systems, including encapsulation, nanoparticles and hydrogels, have significantly enhanced the stability, bioavailability and targeted action of nutraceuticals [16]. While preclinical evidence is compelling, robust clinical validation through well-designed randomized controlled trials is required to establish standardized dosage, safety and efficacy profiles [17].

The purpose of this review is to present a comprehensive synthesis of diabetic wound management strategies, with particular emphasis on the emerging role of nutraceuticals. The discussion highlights risk factors, complications, underlying pathophysiology, conventional allopathic approaches and nutraceutical interventions, thereby underscoring their potential integration into future therapeutic frameworks.

2. Causes and risk factors

The development of diabetic wounds, particularly foot ulcers, is multifactorial, involving metabolic, vascular, neuropathic, immunological and behavioral components. Persistent hyperglycemia is the central driver, inducing structural and functional alterations in nerves, blood vessels and immune cells [10,18].

Peripheral neuropathy is one of the most critical risk factors, affecting up to 50% of individuals with diabetes. Neuropathy diminishes protective sensation in the feet, leaving patients vulnerable to unnoticed injuries caused by minor trauma, pressure points or ill-fitting footwear [19,20]. Autonomic neuropathy further aggravates risk by reducing sweating and skin hydration, resulting in dryness and fissuring that predispose to infection [21].

Peripheral arterial disease (PAD), characterized by macrovascular atherosclerosis and microvascular dysfunction, is another major contributor. Impaired blood flow and reduced oxygen delivery hinder tissue repair, cause ischemia and elevate the risk of gangrene [22,23].

Immune dysfunction plays a pivotal role as well. Hyperglycemia impairs neutrophil chemotaxis, phagocytosis and microbial killing, while simultaneously driving chronic low-grade inflammation. This dual effect creates wounds that are more likely to become infected and less likely to heal effectively [18,24].

Mechanical factors such as foot deformities, callus formation and repetitive pressure also predispose to ulceration. Lack of appropriate footwear and inadequate foot care amplify these risks [25,26].

Other systemic risk factors include poor glycemic control, long duration of diabetes, obesity, hypertension, dyslipidemia and smoking, all of which exacerbate vascular dysfunction and tissue damage [27,28].

Socioeconomic and behavioral determinants are important yet often overlooked. Limited access to healthcare, poor patient education, delayed wound recognition and non-adherence to preventive strategies frequently result in late-stage presentation and poor outcomes [29,30].

Collectively, these interrelated risk factors underscore the necessity of multidisciplinary prevention and management approaches for diabetic wounds.

3. Complications

Diabetic wounds are not only slow to heal but are also associated with serious, often life-threatening complications that impact morbidity, mortality and quality of life.

Infection is the most common complication, arising from impaired immune defenses. Diabetic wounds can rapidly progress from superficial cellulitis to deep tissue involvement, including abscess formation and osteomyelitis, significantly complicating management and increasing the risk of limb loss [2,31,32].

Amputation remains one of the most devastating consequences. Globally, diabetes accounts for nearly 80% of non-traumatic lower-limb amputations, with foot ulcers serving as the precipitating factor in the majority of cases [4,33]. Following an initial amputation, patients face a markedly increased risk of contralateral limb amputation and mortality [34].

Psychological and socioeconomic consequences are equally significant. Patients frequently experience depression, anxiety and social isolation, which may further reduce adherence to medical care [35]. From a health systems perspective, diabetic wound management imposes a multibillion-dollar annual burden in both direct medical costs and indirect losses from disability, absenteeism and reduced productivity [36,37].

Recurrence is another major concern. Even after complete wound closure, recurrence rates remain high—up to 40% within one year and more than 60% within five years [9,38]. This reflects the persistence of underlying neuropathy, vascular disease and biomechanical abnormalities.

Mortality associated with diabetic wounds is alarmingly high, with five-year survival rates estimated at only 50%—a prognosis comparable to many cancers [39].

Thus, the complications of diabetic wounds extend well beyond the local lesion, encompassing systemic decline, psychosocial distress and economic strain. These realities reinforce the need for integrative strategies, including the exploration of nutraceutical-based interventions, to complement conventional therapies.

4. Pathophysiology

The pathophysiology of diabetic wounds is complex and multifaceted, driven primarily by chronic hyperglycemia and its downstream biochemical effects. Elevated glucose levels induce the formation of advanced glycation end-products (AGEs), which accumulate in vascular and connective tissues, altering structural proteins and activating receptors (RAGE) that trigger oxidative stress and chronic inflammation [10,40,41]. Microvascular dysfunction is central to impaired healing. Hyperglycemia causes basement membrane thickening, endothelial dysfunction and capillary rarefaction, reducing tissue perfusion and oxygen delivery [42,43,44]. At the same time, macrovascular disease, including peripheral arterial disease, limits collateral circulation, compounding ischemia [22,45]. Neuropathy contributes to pathophysiology via sensory, motor and autonomic components. Sensory neuropathy diminishes pain perception, increasing the risk of unnoticed trauma. Motor neuropathy alters foot biomechanics, leading to abnormal pressure distribution and ulcer formation, while autonomic neuropathy reduces sweat and oil gland function, resulting in dry, fissured skin [19,21,46]. Immune dysregulation further complicates wound repair. Neutrophils exhibit reduced chemotaxis and phagocytosis, while macrophages remain locked in a pro-inflammatory M1 phenotype rather than transitioning to the reparative M2 type [24,47,48]. This persistent inflammation delays granulation tissue formation and epithelialization. At the molecular level, impaired expression of growth factors such as VEGF, PDGF and TGF-β contributes to delayed angiogenesis and collagen deposition [49,50,51]. Additionally, chronic oxidative stress damages cellular DNA, proteins and lipids, further inhibiting repair mechanisms [52,53,54]. The convergence of ischemia, neuropathy, infection and impaired immune responses leads to chronic, non-healing wounds. This complex interplay explains why diabetic wounds are often refractory to standard therapies and highlights the need for adjunctive strategies like nutraceutical interventions.

5. Conventional medical management

The conventional management of diabetic wounds involves a multidisciplinary approach, integrating systemic and local therapies. Allopathic remedies primarily include drug-based interventions, which can be broadly categorized as follows:

Antidiabetic agents. Optimal glycemic control is the cornerstone of management. Insulin therapy and oral hypoglycemic agents such as metformin, sulfonylureas and sodium-glucose co-transporter-2 (SGLT2) inhibitors help reduce hyperglycemia and mitigate further vascular and neuropathic damage [55,56].

Antibiotics. Broad-spectrum or targeted antibiotics are prescribed to manage and prevent wound infections, particularly against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Drug choices depend on wound cultures and resistance patterns [31,57].

Antiplatelet and anticoagulant drugs. Aspirin, clopidogrel and heparin derivatives are often employed to improve blood flow, reduce thrombotic risk and enhance tissue perfusion [58,59].

Vasoactive and endothelial modulators. Agents such as cilostazol and pentoxifylline are sometimes used to improve microcirculation and reduce intermittent claudication symptoms in patients with peripheral arterial disease [59,60].

Growth factor therapies. Recombinant human platelet-derived growth factor (rhPDGF, becaplermin) has been approved for topical use in diabetic ulcers, although high cost and limited efficacy remain challenges [61,62].

Analgesics and supportive agents. Pain management is important, especially in infected or ischemic wounds. Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics are used cautiously to avoid adverse effects [62,63].Despite these options, standard drug therapy often falls short, particularly in chronic, non-healing wounds. Limitations such as antibiotic resistance, high cost and recurrent ulceration emphasize the need for complementary strategies. This gap provides an opportunity for nutraceutical and nutritional approaches to play a synergistic role in promoting wound healing [64,65].

6. Nutraceutical management

Nutraceuticals have emerged as promising adjunctive strategies for diabetic wound management, targeting multiple aspects of impaired healing such as oxidative stress, inflammation, angiogenesis and collagen deposition. Unlike allopathic therapies, nutraceuticals act via pleiotropic mechanisms and may provide safer, cost-effective options for long-term management [66–68]. Figure 1 shows a diagrammatic representation of causes and risk factors, pathophysiology and nutraceutical interventions in diabetic wound healing.

6.1. Antioxidant vitamins

- **Vitamin C (ascorbic acid).** Vitamin C is essential for collagen hydroxylation and extracellular matrix stabilization. Its deficiency impairs fibroblast proliferation and angiogenesis. Supplementation improves granulation tissue formation and tensile strength in diabetic wounds [69–72].
- **Vitamin E (α-tocopherol).** A lipid-soluble antioxidant, vitamin E protects cell membranes from oxidative stress. Both topical and systemic supplementation enhance epithelialization, reduce lipid peroxidation and improve microvascular circulation [73–75].

6.2. Trace elements

- **Zinc.** Zinc is a cofactor for DNA synthesis and matrix metalloproteinases (MMPs), facilitating keratinocyte migration and re-epithelialization. Oral supplementation and zinc oxide dressings accelerate wound contraction and epithelial regeneration [76–79].
- **Copper.** Copper supports angiogenesis by stimulating vascular endothelial growth factor (VEGF) expression and promoting collagen crosslinking. Copper peptide dressings have accelerated closure of chronic ulcers in studies [80–83].
- **Magnesium.** Magnesium regulates enzymatic activity and protein synthesis. Deficiency impairs fibroblast function, while supplementation enhances tissue repair and reduces inflammation [84–87].

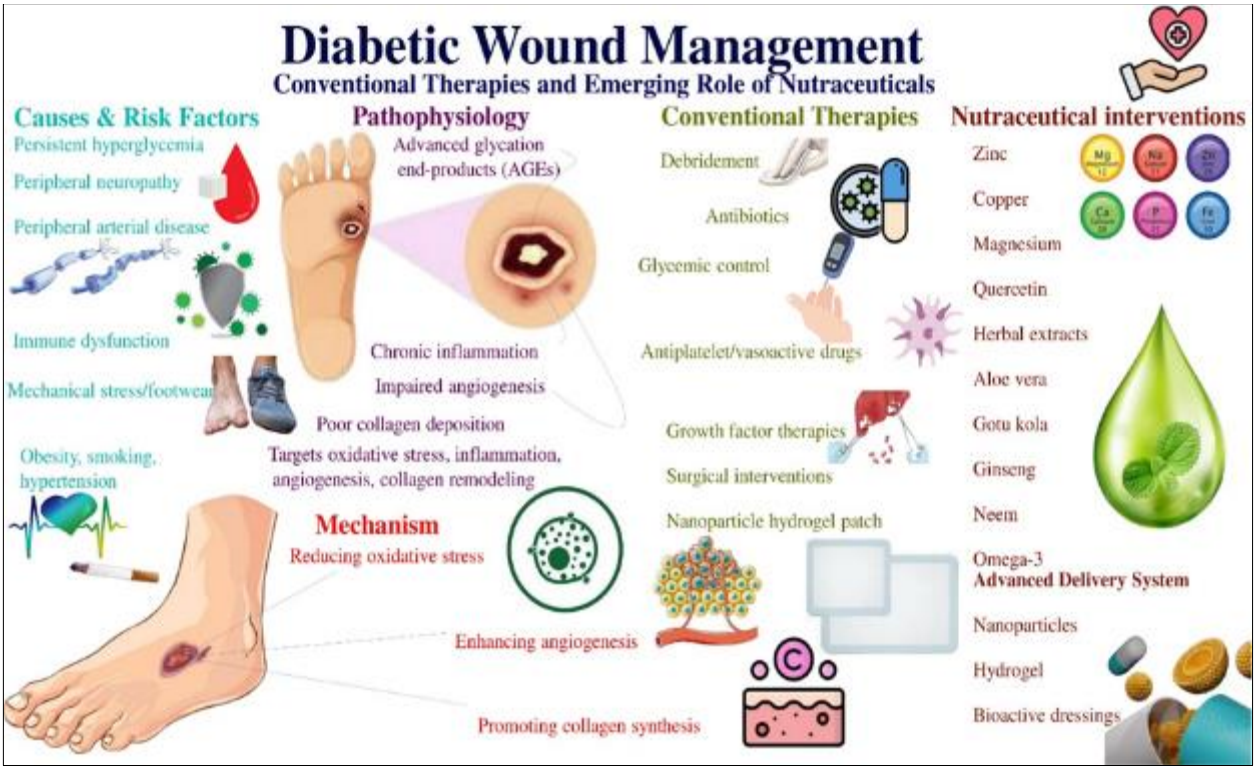

Figure 1 Diagrammatic representation of causes and risk factors, pathophysiology and nutraceutical management

6.3. Amino acids and derivatives

- Arginine. As a substrate for nitric oxide synthase, arginine promotes vasodilation, collagen deposition and immune function. Oral arginine supplementation has been associated with faster healing and increased granulation tissue [88–91].
- Glutamine. A major fuel for fibroblasts and immune cells, glutamine supplementation reduces oxidative stress, enhances collagen synthesis and supports epithelial repair [92–95].
- Ornithine α-ketoglutarate. This derivative enhances collagen deposition and stimulates growth hormone secretion, thereby accelerating wound closure in diabetic models [96–98].

6.4. Polyphenols and flavonoids

- Curcumin. Derived from *Curcuma longa*, curcumin downregulates NF-κB signaling, reduces pro-inflammatory cytokines and enhances angiogenesis. Nanoparticle-based topical formulations have significantly improved healing rates in diabetic models [99–102].
- Resveratrol. A polyphenol in grapes, resveratrol activates SIRT1 and AMPK pathways, reducing oxidative stress and enhancing angiogenesis. Both oral and topical forms have shown benefit [103–106].
- Quercetin. Abundant in onions and apples, quercetin promotes fibroblast proliferation and reduces oxidative damage. Topical quercetin gels accelerate epithelialization [107–110].
- Green tea catechins (EGCG). Epigallocatechin gallate reduces advanced glycation end-products and promotes keratinocyte migration. VEGF upregulation enhances angiogenesis [111–114].

6.5. Omega-3 fatty acids

- Omega-3 fatty acids, particularly EPA and DHA, exert anti-inflammatory effects by modulating eicosanoid production. Supplementation enhances endothelial function, neovascularization and wound closure. Clinical evidence suggests improved microcirculation and tissue repair in humans [115–119].

6.6. Probiotics and prebiotics

- Gut microbiota dysbiosis contributes to impaired healing. Probiotics such as *Lactobacillus* and *Bifidobacterium* strains enhance immune regulation, reduce systemic inflammation and support collagen deposition. Prebiotics like inulin improve gut health and indirectly aid wound repair [120–129].

6.7. Herbal extracts and phytochemicals

- Aloe vera. Topical aloe stimulates fibroblast activity, collagen synthesis and angiogenesis. Clinical studies show shorter healing times in diabetic ulcers [130–134].
- Centella asiatica. Triterpenoids improve collagen remodeling, tensile strength and microvascular circulation [135–139].
- Ginseng. Ginsenosides enhance angiogenesis, modulate glucose metabolism and support wound contraction [140–143].
- Neem (*Azadirachta indica*). Exhibits antimicrobial and antioxidant effects, reducing bacterial colonization and oxidative stress [144–148].

6.8. Advanced nutraceutical delivery systems

Nanoparticles, hydrogels and scaffolds improve the stability, bioavailability and sustained release of nutraceuticals. Examples include curcumin-loaded nanoparticles, zinc oxide dressings and nutraceutical-enriched hydrogels with honey, aloe and chitosan [76,99,130,149–157].

6.9. Combination therapies

Evidence suggests synergistic effects when nutraceuticals are combined. For instance, vitamin C plus zinc supplementation enhances collagen synthesis more than either alone [72,158–160]. Curcumin with resveratrol shows additive anti-inflammatory benefits [161–164].

6.10. Clinical evidence and challenges

Despite strong preclinical evidence, clinical trials remain limited. Small-scale studies with arginine, zinc and antioxidant vitamins show promise, but larger trials are necessary [91,165–167]. Challenges include variability in formulations, poor bioavailability and lack of standardized dosing [168–172]. Future directions involve personalized therapy, integration with standard wound care and novel delivery systems. Nutraceuticals hold potential to transform diabetic wound management by providing safe, adjunctive and cost-effective solutions [173–178].

7. Conclusion

Diabetic wounds remain one of the most debilitating complications of diabetes mellitus, causing severe morbidity, high recurrence and an increased risk of lower-limb amputations. Despite advances in debridement, glycemic control, infection management and surgical interventions, the rate of complete healing remains suboptimal because conventional therapies do not fully address the underlying metabolic, vascular and immune dysfunctions.

Nutraceuticals have emerged as promising adjunctive strategies, offering multifaceted benefits such as antioxidant protection, modulation of inflammation, enhancement of angiogenesis and improved collagen remodeling. Bioactive compounds including vitamins, trace elements, amino acids, polyphenols, omega-3 fatty acids, probiotics and herbal extracts have demonstrated encouraging results in preclinical and clinical studies. Additionally, innovations in delivery systems, such as nanoparticles, hydrogels and combination formulations, have improved their stability, bioavailability and therapeutic potential.

However, challenges persist in translating these findings into routine clinical practice. Variability in formulations, limited large-scale randomized controlled trials and a lack of standardized dosing guidelines remain barriers to widespread application.

Future directions should focus on well-designed clinical studies, personalized nutraceutical-based therapies and integration of these agents with established wound care protocols. By bridging conventional and nutraceutical approaches, diabetic wound management may achieve safer, cost-effective and more effective outcomes, ultimately improving patient survival and quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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