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REVIEW

Advanced Natural Therapeutics and Delivery Strategies for Diabetic Foot Ulcers: A Mini Review

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Abstract: Diabetic foot ulcers (DFUs) are a severe complication of diabetes mellitus with complex pathophysiology. Conventional therapies often lead to poor healing and high recurrence. This mini-review highlights the promise of advanced natural therapeutics and delivery strategies for DFU management. We focus on bioactive natural compounds, such as ginsenosides, astragalus polysaccharides, and resveratrol, that target critical processes like hyperglycemia, vascular impairment, and oxidative stress by modulating key signaling pathways. To improve bioavailability, innovative delivery systems including nanotechnology and nitric oxide-releasing platforms have been developed, enabling sustained release and enhanced healing. Clinical evidence shows promising results, such as shortened healing time and improved ulcer closure rates, supports the translational potential of standardized natural formulations. Moving forward, priorities should focus on standardizing natural formulations, optimizing delivery, and conducting rigorous clinical trials. With continued innovation, natural therapeutics hold significant potential to improve wound healing, reduce amputations, and enhance the quality of life for DFU patients.

Keywords: diabetic foot ulcers, natural therapeutics, bioactive compounds, wound healing, nanotechnology

Introduction

Diabetic foot ulcers (DFUs) represent a critical complication of diabetes mellitus and pose a significant global healthcare challenge. Globally, over 550 million people live with diabetes, including 37 million in the United States.[1] Approximately 18.6 million new DFU cases occur annually, affecting about 34% of the diabetic population. DFUs are chronic, non-healing wounds that predominantly occur on the feet, driven by a multifactorial etiology including hyperglycemia-induced peripheral neuropathy, tissue ischemia and impaired angiogenesis due to peripheral arterial disease, and dysregulated chronic inflammation with compromised immune defense.[2] The impact of DFUs is profound, resulting in substantial disability-adjusted life years (DALYs) lost and healthcare costs amounting to billions of dollars annually.[3] DFU management accounts for a significant portion of diabetes-related expenditures, driven by high hospitalization rates and prolonged treatments. Moreover, DFUs are a leading cause of lower limb amputations, with approximately 20% of diabetic patients with foot ulcers requiring amputation, either partial or complete.[4,5] In the United States alone, over 150,000 non-traumatic lower limb amputations are performed annually, contributing to a global total of 1.6 million amputations, of which 33% involve complete limb loss.[6,7] These factors collectively underscore the urgent need for innovative therapeutic strategies to alleviate the socioeconomic impact of DFUs on both patients' quality of life and healthcare systems.

Standard management of DFUs has traditionally relied on practices such as debridement, infection control, and offloading pressure from the affected area.[8] However, these conventional therapies often prove insufficient, as many patients experience slow or incomplete wound healing, which significantly compromises their recovery.[9] The high recurrence rate of DFUs, which can be as high as 60%, further highlights the limitations of current standard-of-care, which frequently fails to address the underlying pathological mechanisms such as persistent inflammation, microvascular

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dysfunction, and cellular senescence. This therapeutic failure poses ongoing risks to patients' health and quality of life.[10] This persistent clinical challenge underscores the urgent need for innovative therapeutic approaches that can effectively target the multifaceted pathophysiological mechanisms of DFUs, particularly those related to impaired tissue regeneration and chronic inflammation.[11]

Given these unmet needs, there is growing interest in exploring alternative and adjunctive therapies. Recent advancements in natural therapeutics have opened new avenues for DFUs management by combining bioactive compounds with cutting-edge delivery technologies.[12,13] Phytochemicals, a diverse group of naturally occurring compounds found in plants such as fruits, vegetables, grains, and other plant foods, have emerged as promising therapeutic agents due to their multi-targeted actions.[14] Preclinical, clinical, and epidemiological studies suggest that phytochemicals may be effective in treating various diseases owing to their anti-inflammatory, antioxidant, and pro-angiogenic activities.[15] However, challenges such as poor bioavailability, chemical instability, and limited tissue penetration have historically constrained their clinical application. To overcome these barriers, nanotechnology-driven strategies have been employed to enhance their therapeutic potential. For instance, nano-encapsulation of active ingredients enables sustained release, targeted delivery to wound sites, and improved cellular uptake.[16,17] These innovations not only optimize pharmacokinetics but also amplify key healing processes such as collagen synthesis, macrophage polarization, and angiogenesis.

Therefore, this mini-review aims to synthesize current mechanistic evidence and translational opportunities for advanced natural therapeutics in DFUs care. The potential of these agents is explored, focusing on their ability to target critical pathological processes, including hyperglycemia, peripheral neuropathy, vascular insufficiency, persistent inflammation, wound infection, and oxidative stress. Furthermore, supplementary strategies, such as nanocarriers and nitric oxide (NO)-releasing gels, are discussed for their role in enhancing therapeutic efficacy. While clinical trials demonstrate promising translational progress, challenges related to standardization and scalability remain. By integrating mechanistic insights with therapeutic advancements, this review highlights the transformative potential of natural compounds in redefining DFU management.

Pathophysiology of Diabetic Foot Ulcers

Hyperglycemia-Induced Neuropathy

Diabetic peripheral neuropathy (DPN) is a critical factor in the pathogenesis and progression of diabetic foot complications and is strongly associated with lower limb ulcers, amputations, and disability.[18] One of its core clinical consequences is severe impairment of sensory nerve function, coupled with autonomic neuropathy leading to dysfunction in sweat gland secretion.[19] Neuropathy-induced sensory deficits, particularly in pain perception, significantly elevate the risk of trauma in diabetic patients. Alarmingly, this sensory impairment often leads to delayed detection of skin injuries and ulcers, which may remain unnoticed by both patients and healthcare providers for weeks or even months, resulting in inadequate and untimely intervention.[20]

Persistent hyperglycemia, typically defined as blood glucose levels exceeding 180 mg/dL, drives nerve damage through a complex interplay of mechanisms. Firstly, it induces metabolic dysregulation, characterized by the accumulation of fructose and sorbitol and a decline in myo-inositol levels.[21] This metabolic imbalance triggers osmotic disturbances, including sodium and water retention, as well as reduced Na^+, K^+-ATPase activity, which directly injures neurons. Secondly, glucose overload exacerbates mitochondrial dysfunction, leading to the generation of excessive reactive oxygen species (ROS) that damage Schwann cell DNA and impair the axonal transport of neurotrophic factors.[22] In an oversaturated system, acetyl-CoA converts to acylcarnitine, inducing stress in Schwann cells and dorsal root ganglion (DRG) neurons while further exacerbating mitochondrial dysfunction, ultimately resulting in axonal degeneration.[23] Thirdly, hyperglycemia degrades type IV collagen within the basement membrane of nerve-nourishing blood vessels and disrupts the distribution of aquaporins on astrocyte end-feet, compromising the glio-vascular interface and exacerbating nerve ischemia.[24] Collectively, these processes impair axonal conduction, signal transmission, and neurotrophic support, culminating in centripetal degeneration and distal axonal length-dependent loss.

Ischemic-Vascular Pathology

Diabetes induces widespread ischemic vascular pathology by damaging both macro- and microvascular systems, posing a severe threat to peripheral nerves and wound healing. Chronic hyperglycemia is the central driver of these vascular complications.[25] At the macrovascular level, it accelerates atherosclerosis through mechanisms involving hyperglycemia, insulin resistance, excess free fatty acids, and advanced glycation end products (AGEs).[26] These factors collectively suppress endothelial nitric oxide synthase (eNOS) activity, increase ROS production, and activate pro-inflammatory transcription factors such as NF-κB and aquaporin 1.[27] This inflammatory cascade promotes leukocyte adhesion, migration, and lipid uptake by macrophages, leading to foam cell formation and atherosclerotic plaque development. Atherosclerosis, affecting large arteries, is a primary cause of cardiovascular disease, stroke, and peripheral arterial disease (PAD). PAD, in turn, impairs distal limb perfusion, contributing to approximately 50% of DFUs, while delaying wound healing and increasing infection risks.[28]

At the microvascular level, diabetes triggers characteristic microangiopathy, involving small arteries and capillaries, which underpins nephropathy, retinopathy, and DPN. Endothelial injury initiates microvascular dysfunction, causing hemodynamic abnormalities, impaired oxygen delivery, and fluid filtration imbalance.[29] Damage to the vasa nervorum, the microvessels supplying nerves, is particularly critical, reducing blood flow to neural tissues.[30] This manifests as impaired intraneural hemodynamics, loss of autoregulation, and structural abnormalities such as basement membrane thickening, endothelial cell swelling, and reduced tight junction proteins. These changes lead to vessel narrowing, increased resistance, and chronic ischemia, contributing to DPN pathogenesis.[31]

Thus, diabetic vascular pathology creates a vicious cycle of macrovascular occlusion and microvascular dysfunction, exacerbated by vasoconstriction and hypercoagulability. This not only elevates ulcer risk but also impedes wound healing by depriving tissues of oxygen and nutrients, ultimately leading to non-healing ulcers and catastrophic outcomes like amputations.[32]

Inflammation-Infection Vicious Cycle

In diabetic patients, skin barrier disruption facilitates bacterial invasion, initiating a complex interplay between infection and a maladaptive host inflammatory response that is central to the pathophysiology of DFUs.[33] Unhealed ulcers provide an ideal environment for polymicrobial infections. Gram-positive bacteria (eg, *Staphylococcus aureus, Streptococcus species*) often dominate superficial wounds, while Gram-negative bacteria colonize deeper abscesses. Mixed infections, involving bacteria (eg, *coagulase-negative staphylococci, enterococci, anaerobes*) and fungi (eg, *Candida albicans, Candida parapsilosis*), complicate treatment, impair healing, and increase the risk of chronic wounds and scarring.[34]

Chronic inflammation is a central barrier to DFU healing.[35] Even before skin breakdown, endogenous damage in diabetic feet is linked to abnormal inflammatory cytokine levels. Persistent inflammation disrupts the epidermal microenvironment, impairs cellular repair, exacerbates hyperglycemia, and increases insulin resistance.[36] Hyperglycemia itself compromises immune function, reducing monocyte counts, disrupting T-cell subsets, and impairing phagocytic activity in neutrophils and macrophages, while promoting excessive inflammatory cytokine release.[37] During wound healing, macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes is critical for resolving inflammation.[38] However, in DFUs, macrophage dysfunction and impaired polarization perpetuate a pro-inflammatory state, delaying repair.

Immune cell dysfunction exacerbates the inflammation-infection cycle. Diabetic wounds exhibit impaired neutrophil chemotaxis, phagocytosis, degranulation, and ROS production, further compromised by hyperglycemia-induced upregulation of protein arginine deiminase 4 and inhibition of neutrophil extracellular trap formation. This weakens antimicrobial defense and promotes tissue damage through excessive cytokine and protease release.[39,40] This dysfunction is compounded by a protease imbalance caused by activated macrophages and neutrophils, which secrete proteases such as MMPs that degrade extracellular matrix proteins, including collagen, elastin, and fibronectin. The resulting fragments recruit inflammatory cells, sustain inflammation, and activate additional MMPs, creating a destructive feedback loop.[41] Additionally, diabetic wounds suffer from immune dysregulation, characterized by disrupted collaboration between immune cells, such as macrophages, neutrophils, and lymphocytes, and repair cells, including keratinocytes, fibroblasts, and endothelial cells, which collectively undermines the healing process.[42,43]

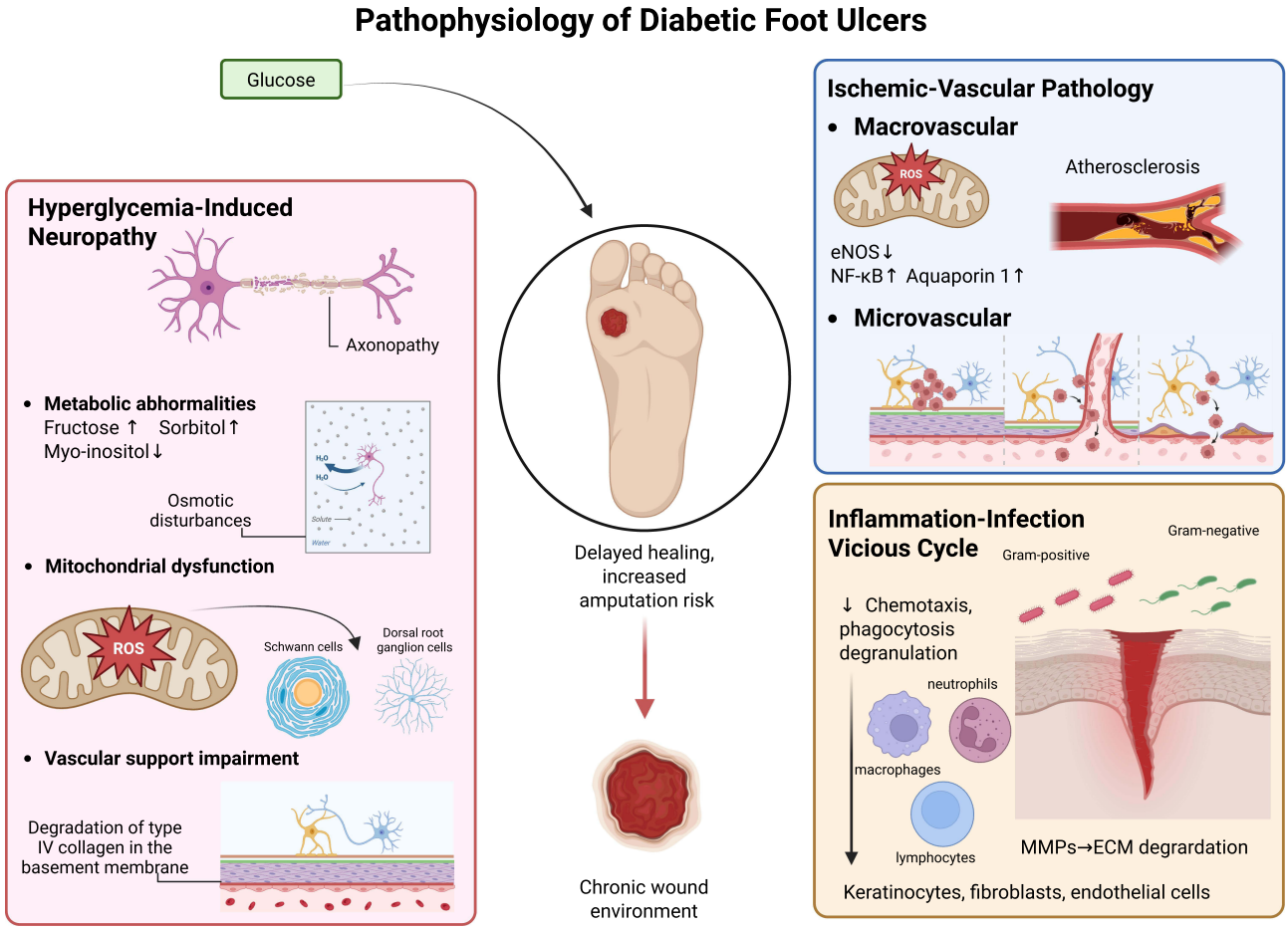

Figure 1 Pathophysiology of Diabetic Foot Ulcers.

Thus, DFUs are trapped in a self-perpetuating inflammation-infection cycle: hyperglycemia and initial injury trigger chronic inflammation and immune suppression, increasing infection susceptibility. Persistent infections, in turn, activate dysfunctional immune cells that release destructive mediators, further impeding healing and maintaining a non-healing wound environment. Breaking this cycle is therefore a primary therapeutic objective in DFU management. Figure 1.

Current Treatment Strategies for Diabetic Foot Ulcers

The treatment strategies for DFUs require a comprehensive approach that directly addresses the complex pathophysiology, outlined in Pathophysiology of Diabetic Foot Ulcers, including hyperglycemia-induced neuropathy, ischemic-vascular pathology, and the inflammation-infection vicious cycle.

Management of Hyperglycemia-Induced Neuropathy

Strict glycemic control is the cornerstone of DPN management, with pancreatic transplantation showing significant efficacy in normalizing blood glucose and improving motor and sensory neuropathy.[44] For pharmacological treatment, pregabalin, tapentadol, and duloxetine are FDA-approved for alleviating DPN-related pain.[45] Additionally, antioxidants such as alpha-lipoic acid (ALA) have shown potential in delaying or reversing peripheral nerve damage.[46] Stem cell therapy and low-dose IL-6 biotherapy are also under exploration, offering new directions for DPN treatment by promoting angiogenesis and neuroprotection.[47,48]

Intervention for Ischemic-Vascular Pathology

Ischemic vascular pathology is a major barrier to DFU healing. Revascularization techniques, such as bypass surgery and endovascular angioplasty, are primary methods for restoring blood flow.[49,50] While atherectomy can remove atherosclerotic plaques, its efficacy has not been proven superior to angioplasty.[51] Postoperative multidisciplinary care, including the management of hypertension and hypercholesterolemia, is crucial for successful outcomes. Hyperbaric oxygen therapy (HBOT) enhances tissue oxygenation by increasing plasma oxygen levels, significantly boosting physically dissolved oxygen.[52] According to Fick's law, elevated oxygen partial pressure enhances the driving force and diffusion distance of oxygen, accelerating ulcer healing. Furthermore, HBOT activates the hypoxia-inducible factor (HIF-1α) signaling pathway, promoting the expression of vascular endothelial growth factor (VEGF) and improving local blood supply, thereby providing the oxygen and nutrients necessary for tissue repair.[53,54]

Control of the Inflammation-Infection Vicious Cycle

Given the critical role of the inflammation-infection cycle described in the previous section, its control is paramount in DFU management. Infection control is a critical component. The choice of empirical antibiotic therapy should be selected based on the likely pathogens and the severity of the infection.[55] Mild infections may be treated with dicloxacillin or cephalexin, moderate infections with vancomycin combined with ampicillin/sulbactam, and severe infections with broad-spectrum antibiotics such as piperacillin/tazobactam or carbapenems. HBOT enhances the antibacterial effects of antibiotics by promoting bacterial aerobic metabolism and increasing drug uptake.[56] Additionally, HBOT induces the production of oxygen free radicals, directly damaging bacterial membrane proteins and DNA structures, inhibiting the generation of inflammatory factors, and promoting the resolution of inflammation at the infection site.[57]

Debridement is a crucial component of infection management, as it removes bacterial biofilms and necrotic tissue from the wound, creating favorable conditions for healing.[58] Wound debridement and cleansing are typically performed using isotonic saline solution and are essential adjuncts to antibiotic therapy. Wound dressings, such as hydrogels,[59] alginate dressings,[60] hydrocolloids,[61] foam adhesives,[62] and hydrofibers,[63] protect the wound from infection and environmental exposure while maintaining optimal moisture levels to promote new tissue formation and autolytic debridement.

Advanced Natural Therapeutics for Diabetic Foot Ulcers

Key Bioactive Compounds and Mechanisms

Advanced natural therapeutics address the core pathophysiological mechanisms of DFUs through multifaceted approaches. Of particular relevance is their potential to disrupt the persistent inflammation-infection cycle that profoundly impedes healing.

Immunomodulatory and Anti-Inflammatory Mechanisms

Inflammation and infection control are addressed through the modulation of innate immune responses, directly targeting pathways involved in the vicious cycle. Bletilla striata polysaccharide (BSP) inhibits NLRP3 inflammasome activation, targeting a key driver of chronic inflammation in DFUs.[64] Puerarin suppresses NF-κB and MAPK signaling pathways and promotes macrophage polarization towards the reparative M2 phenotype.[65] Astragalus polysaccharide shifts macrophage polarization via β-catenin/NF-κB and Nrf2/HO-1 pathways, significantly reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12.[66,67] Resveratrol exhibits broad anti-inflammatory effects, inhibits the AGE-RAGE pathway and promotes healing via PI3K/Akt signaling.[68,69]

In summary, the immunomodulatory actions of these natural compounds are pivotal for breaking the inflammation-infection cycle in DFUs. By targeting key inflammatory signaling hubs and promoting a pro-resolving macrophage phenotype, they help resolve chronic inflammation, reduce tissue damage, and create a microenvironment conducive to healing. This represents a fundamental shift from merely suppressing infection to actively reprogramming the dysfunctional immune response.

Glucose-Lowering and Neuropathy-Targeting Mechanisms

Beyond inflammation control, these therapeutics also target other key pathological axes, primarily hyperglycemia reduction and neuropathy improvement. Gomisin A enhances insulin sensitivity and accelerates wound healing by suppressing the neuroinflammatory TLR4/p38 MAPK/IL6 pathway.[70] Similarly, the ethanolic extract of *Euphorbia hirta* demonstrates dual efficacy by reducing hyperglycemia and oxidative stress markers such as malondialdehyde and NO while promoting wound closure.[71]

Collectively, targeting hyperglycemia and associated neuropathic pathways addresses the root cause of DFU development. By improving glycemic control and directly protecting nerves from glucotoxic insults, these compounds can prevent initial ulceration and improve sensory function, thereby reducing the risk of unnoticed trauma, a critical factor in DFU pathogenesis.

Pro-Angiogenic Mechanisms

For alleviation of vascular lesions and impaired angiogenesis, several compounds exhibit potent activity. Ginsenoside Rg1, which promotes endothelial cell function and neovascularization, acts through PI3K/Akt/eNOS signaling and modulates microRNAs including miR-489-3p/Sirt1 and miR-23a/IRF-1.[72–74] Ramulus Mori alkaloids (SZ-A) protect endothelial cells from oxidative damage and stimulate angiogenesis via the NRF2/HO-1/eNOS axis.[75] β-sitosterol activates MAPK/mTOR/VEGF pathways, enhancing microvascular perfusion,[76] while Astragalus aqueous extract upregulates HIF-1α and VEGF expression, directly counteracting tissue ischemia.[77]

The core significance of these pro-angiogenic agents lies in their ability to reverse tissue ischemia, a major barrier to healing in DFUs. By activating critical pathways that drive the formation of new blood vessels and enhancing endothelial cell survival, they improve the delivery of oxygen and nutrients to the wound bed, which is essential for supporting the cellular activities required for tissue repair.

Antioxidant Mechanisms

Moreover, oxidative stress mitigation represents another critical therapeutic axis. Resveratrol alleviates hyperglycemia-induced ferroptosis in endothelial cells by regulating Nrf2 activity and key markers such as GPX4, SLC7A11, and ACSL4.[78] Dracorhodin activates the Nrf2 pathway while inhibiting ferroptosis, reducing ROS and promoting repair.[79] Narirutin reprograms cellular metabolism via the AMPK/Mfn2 pathway, reducing oxidative damage and inflammation.[80]

The antioxidant mechanisms, particularly those involving the Nrf2 pathway, are crucial for mitigating oxidative damage that perpetuates cellular dysfunction and death in the diabetic wound environment.

Nanotechnology and Hydrogel-Based Delivery Systems

To overcome bioavailability limitations, nanotechnology-driven delivery systems have been developed to enhance therapeutic potential. Gallium-modified gelatin nanoparticles loaded with quercetin, which promote sustained release and TGF-β/Smad-mediated M2 macrophage polarization, accelerate repair while inhibiting scar formation.[81] Curcumin nanoparticle hydrogel (Cur-NP/HG), which outperforms conventional formulations, enhances re-epithelialization and collagen deposition while reducing inflammation.[82] Chitosan nanogel encapsulating Teucrium polium nanoparticles (TP-NP/CS-NG), which improves stability and bioavailability, effectively alleviates oxidative stress and promotes angiogenesis.[83]

A cutting-edge metal-polyphenol nanocomposite hybrid hydrogel has been developed for DFU microenvironment reprogramming.[84] Composed of EGCG/Fe^{3+} nanoparticles loaded with salvianolic acid B and glucose oxidase within a polysaccharide hydrogel, it exhibits potent antibacterial activity, promotes M2 macrophage polarization, angiogenesis, and ROS scavenging, significantly accelerating wound healing. NO-releasing gels represent a sophisticated strategy that combines natural compounds with gaseous signaling molecules. Asiaticoside-NO gel, which enhances healing via Wnt/β-catenin signaling, increases VEGF, iNOS, eNOS, and CD34 expression while exerting antimicrobial effects.[85] Asiaticoside-NO hydrogel (ACNO), which modulates critical metabolic pathways such as methyl histidine metabolism and the malate-aspartate shuttle, attenuates SRC/STAT3 activation to promote repair.[86] Centella asiatica total glycosides-

NO gel (CATGNOG), which provides a stable and non-toxic delivery platform, demonstrates significant clinical potential.[87]

Multicomponent Hydrogels synergize bioactive properties. The BSP/Berberine hydrogel, which achieves 94.9% ± 1.81% wound closure in diabetic mice by day 14, combines antibacterial, anti-inflammatory, and antioxidant actions.[88]

Preclinical and Clinical Evidence

Robust clinical evidence supports ON101, a standardized blend of Plectranthus amboinicus PA-F4 and Centella asiatica S1. A multicenter, randomized controlled trial demonstrated a significantly higher complete healing rate with ON101 cream (60.7%) versus absorbent dressing (35.1%) over 16 weeks, with an odds ratio of 2.84 and a 95% confidence interval of 1.66–4.84.[89] Post-hoc analysis confirmed efficacy in high-risk patients, including those with Wagner grade 2 ulcers, size ≥5 cm^2, duration ≥3 months, HbA1c ≥9%, and BMI ≥25.[90] Teucrium polium ointment, which significantly enhances healing of non-infected DFUs, has also been validated in a randomized clinical trial.[91] Table 1.

Challenges and Future Perspectives

Comparative Analysis and Therapeutic Modalities

A critical evaluation of the different natural product classes and delivery systems reveals distinct advantage and niches for each, which is crucial for guiding future research and clinical application. Flavonoids and polyphenols, including quercetin, puerarin, resveratrol, and curcumin, are particularly notable for their potent antioxidant and anti-inflammatory activities, primarily mediated through the Nrf2 and NF-κB pathways. In contrast, polysaccharides such as Astragalus polysaccharide and BSP exhibit superior immunomodulatory effects, excellent water solubility, and biocompatibility, making them ideal for hydrogel-based dressings. Saponins, exemplified by Ginsenoside Rg1, demonstrate remarkable pro-angiogenic efficacy via pathways like PI3K/Akt/eNOS.

Regarding delivery platforms, nanocarriers, such as nanoparticles and nanogels, excel in protecting labile compounds, enabling targeted and sustained release to specific wound cells, and enhancing penetration into wound beds. Hydrogel systems provide a moist wound-healing environment, are ideally suited for topical application, and can be designed to respond to wound microenvironment cues. The emerging trend of embedding nanocarriers within hydrogels represents a promising synergy, combining the protective and targeted delivery advantages of nanotechnology with the practical application and sustained reservoir benefits of hydrogels. Table 2.

Translational Challenges and Standardization Hurdles

Despite promising preclinical and early clinical results, significant translational challenges hinder the widespread adoption of natural therapeutics for DFUs. Standardization and quality control remain critical obstacles due to variability in plant sourcing, extraction methodologies, and active compound content.[157,158] Rigorous phytochemical standardization using advanced analytical techniques such as HPLC and LC-MS, along with the establishment of pharmacopeial standards, is essential to ensure batch-to-batch consistency and meet regulatory requirements.

Challenges in bioavailability and delivery optimization persist. While advanced systems such as nanoparticles and NO-gels show promise, achieving effective drug concentrations in deep, ischemic ulcer beds requires further engineering. It is also important to note that the current body of literature, including this review, leans towards reporting positive preclinical outcomes. A more balanced perspective for the field requires increased publication and discussion of negative, inconclusive, or contradictory findings to fully assess therapeutic potential and avoid publication bias. Key priorities include improving the physicochemical properties and reproducibility of nanomaterials for clinical applications, as well as addressing uncertainties regarding their biodistribution, degradation, and long-term biological effects.[16] Additionally, more in vivo studies in large animal models are needed, as current research predominantly relies on rodent models that imperfectly replicate human DFU pathophysiology. Developing simpler, more controllable, and reproducible delivery systems is essential to facilitate translation. Furthermore, more specific and convenient administration methods should be explored to enhance efficacy and clinical practicality.

Table 1 Advanced Natural Therapeutics for Diabetic Foot Ulcers

Drug	Study Type	Main Outcomes	Conclusions	References
Dracorhodin	In vitro (HUVECs)	• Accelerated healing • Enhanced collagen synthesis and angiogenesis • Activated Nrf2 pathway	Promotes DFU healing through antioxidant mechanisms and anti-ferroptosis.	[79]
Irisin	In vitro (HUVECs)	• Restored cell viability • Inhibited apoptosis • Promoted migration and angiogenesis	Protects against high glucose-induced endothelial cell injury and promotes angiogenesis.	[92]
Peptide compounds of Wuguchong	In vitro	Promoted endothelial cell proliferation and angiogenesis.	Demonstrates therapeutic potential for diabetic ulcers by promoting angiogenesis.	[93]
Poria cocos (Schw). Wolf triterpenoid extract (PTE)	In vitro	• Promoted angiogenesis • Reduced inflammation • Fostered M2 polarization via PI3K-AKT.	Treats diabetic ulcers by activating PI3K-AKT pathway, demonstrating potential.	[94]
Shikonin	In vitro	• Promoted angiogenesis • Inhibited high glucose-induced endothelial cell dysfunction.	Treats diabetic wounds by targeting multiple pathways, promoting angiogenesis.	[95]
Gomisin A	In vivo (Mouse)	• Accelerated wound healing • Improved insulin sensitivity • Suppressed neuroinflammation	Promotes diabetic wound healing by modulating metabolism and inflammation.	[70]
Euphorbia hirta ethanolic extract	In vivo	• Enhances wound closure • Reduces blood glucose • Reduces oxidative stress	Facilitates diabetic wound healing through hypoglycemic and antioxidant effects.	[71]
Ginsenoside Rg1	In vitro (HUVECs) In vivo (DFU model)	• Promotes angiogenesis • Enhanced endothelial cell function via PI3K/Akt/eNOS signaling	Alleviates DFUs primarily by enhancing vascularization.	[72]
Ginsenoside Rg1	In vivo (Rat) In vitro (HUVECs)	Accelerated wound healing by enhancing NO signaling and VEGF expression	Enhances diabetic would healing through NO-mediated angiogenesis.	[73]
Ginsenoside Rg1	In vivo (mouse) In vitro (HUVECs)	• Promoted angiogenesis • Reduced oxidative stress	Enhances DFUs healing by improving vascular function and reducing oxidative damage.	[74]

Ramulus Mori alkaloids (SZ-A)	In vivo In vitro	• Protected endothelial cell from oxidative stress via NRF2/HO-1/eNOS pathway • Accelerated angiogenesis.	A therapeutic candidate by enhancing endothelial cell function and antioxidant defense.	[75]
β-sitosterol	In vivo	• Promoted angiogenesis • Enhanced M2 macrophage polarization • Stimulated collagen synthesis	Accelerates healing by pro-angiogenic and immunomodulatory mechanisms.	[76]
Astragalus aqueous extract	In vivo (Rat)	• Accelerated ulcer healing • Upregulated HIF-1α/VEGF • Reduced inflammation	Promotes DFU healing by improving tissue ischemia and reducing inflammation.	[77]
Bletilla striata polysaccharide (BSP)	In vivo (Mouse)	• Accelerated wound healing • Suppressed NLRP3 inflammasome Improved insulin sensitivity	Promotes DFU healing by inhibiting inflammasome activation and improving metabolism.	[64]
Puerarin	In vivo (Mouse) In vitro (RAW264.7 cells)	• Promoted M2 macrophage polarization • Inhibited NF-κB and MAPK signaling pathways	Enhances healing by modulating immune response towards a pro-repair phenotype.	[65]
Astragalus polysaccharide	In vivo (Rat)	• Promoted M2 macrophage polarization via β-catenin/NF-κB axis • Reduced excessive inflammation	Accelerates diabetic wound healing by resolving chronic inflammation.	[66]
Astragalus polysaccharide	In vivo (Rat) In vitro (THP-1 and HUVECs)	• Inhibited M1 and promoted M2 polarization via Nrf2/HO-1 pathway • Improved vascular function	Ameliorates diabetic vascular dysfunction by modulating macrophage polarization.	[67]
Resveratrol	In vivo In vitro	• Promoted M2 macrophage polarization, Increased collagen deposition • Reduced inflammation via PI3K/Akt	Accelerates healing through anti-inflammatory and tissue-reparative effects.	[68]
Resveratrol	In vivo	• Inhibited AGE-RAGE signaling pathway • Reduced inflammation • Promoted healing	Treats diabetic wounds via multi-targeted action against key pathological pathways.	[69]
Resveratrol	In vivo In vitro	• Alleviated ferroptosis in endothelial cells Promoted angiogenesis • Accelerated healing	Promotes healing by inhibiting ferroptosis and protecting vascular endothelium.	[78]

(*Continued*)

Table 1 (Continued).

Drug	Study Type	Main Outcomes	Conclusions	References
Narirutin	In vitro In vivo	Promoted M2 macrophage repolarization by activating AMPK/Mfn2 axis.	Accelerates healing by reprogramming cellular metabolism and immune response	[80]
Quercetin-loaded gelatin nanoparticles	In vitro (Fibroblasts) In vivo (Rat)	• Promoted M1-to-M2 polarization via TGF-β/Smad signaling • Accelerated repair	Enhances healing and scar-free repair by modulating immune microenvironment	[81]
Curcumin nanoparticle hydrogel (Cur-NP/HG)	In vivo	• Enhanced re-epithelialization • Enhanced collagen deposition • Promoted VEGF expression.	Nano-encapsulation significantly improves the healing efficacy of curcumin.	[82]
Teucrium polium nanopreparation (TP-NP) in chitosan nanogel (CS-NG)	In vivo (Rat)	• Accelerated healing • Enhanced collagen synthesis • Reduced oxidative stress and inflammation	Nano-gel system enhances healing efficacy through comprehensive actions	[83]
Metal-polyphenol nanocomposite hybrid hydrogel (EGCG/Fe^3+-SAB-GOx)	In vitro In vivo (Rat)	• Antibacterial • Enhanced mitochondrial metabolism • Induced M2 polarization • Promoted angiogenesis • Reduced ROS	Reprogrammed metabolic microenvironment for comprehensive DFU therapy.	[84]
Asiaticoside-NO hydrogel (ACNO)	In vitro In vivo	• Accelerated healing • Exhibited antimicrobial effects • Increased angiogenic factors.	Promotes healing via Wnt/β-catenin signaling and antimicrobial activity	[85]
ACNO	In vitro In vivo	• Modulated metabolic pathways • Enhanced angiogenesis • Attenuated SRC/STAT3 pathway	Demonstrates therapeutic potential by targeting metabolic dysregulation	[86]
Centella asiatica total glycosides-NO gel (CATGNOG)	In vitro In vivo	• Accelerated healing • Inhibited bacterial growth • Alleviated inflammation.	A stable and effective therapeutic gel for DFUs.	[87]
BSP/Berberine hydrogel	In vitro In vivo	• Achieved high wound closure rate • Antibacterial • Anti-inflammatory.	A potential clinical dressing due to its multifunctional properties	[88]
Ginkgo biloba extract cream	In vivo	• Enhanced wound closure • Increased collagen synthesis	A promising topical treatment for diabetic wound management.	[96]

Cinnamomum zeylanicum extract	In vivo	• Enhanced wound contraction • Increased collagen synthesis • Exhibited antioxidant defenses.	Promotes healing by modulating MMPs and oxidative stress.	[97]
Cinnamomum verum hydroethanolic extract	In vivo (Mouse)	• Enhanced wound contraction • Promoted fibroblast proliferation • Increased collagen deposition.	Topical application accelerates wound healing in diabetic mice.	[98]
Baicalin	In vivo (Rat)	• Accelerated healing • Upregulated angiogenesis-related factors (VEGF, Ang-1)	A potential therapeutic candidate for DFUs due to its pro-angiogenic properties.	[99]
Hesperidin	In vivo (Rat)	• Accelerated healing • Upregulated angiogenic factors • Reduced oxidative stress	Promotes wound healing in DFUs by enhancing angiogenesis and reducing oxidative stress	[100]
20(S)-Protopanaxadiol	In vitro In vivo	• Promoted angiogenesis • Activated PI3K/Akt/mTOR pathways Increased VEGF	Stimulates angiogenesis and accelerates wound healing via HIF-1α-mediated VEGF.	[101]
Angelica dahurica	In vitro In vivo	• Promoted angiogenesis • Activated PI3K/Akt pathway • Increased PDGF-β expression	Enhances wound healing in DFUs by promoting angiogenesis.	[102]
Angelica dahurica ethanolic extract	In vitro Ex vivo In vivo	• Promoted angiogenesis • Activated ERK1/2, Akt, Enos • Increased NO production.	Accelerates diabetic wound healing by inducing angiogenesis.	[103]
Cryptotanshinone	In vitro In vivo	• Accelerated wound closure • Enhanced angiogenesis • Suppressed inflammation	A potential therapeutic agent for diabetic wound healing.	[104]
Sanguisorba officinalis L. ethanol extract	In vitro In vivo	• Improved healing rate • Reduced pro-inflammatory cytokines Modulated M1/M2 polarization.	A promising treatment due to anti-inflammatory effects and macrophage modulation.	[105]
DT-13 (from Liriope spicata Lour).	In vitro In vivo	• Promoted wound healing • Modulated macrophage polarization (M1 to M2) • Enhanced angiogenesis.	A promising therapeutic agent due to anti-inflammatory and pro-angiogenic effects.	[106]

(*Continued*)

Table 1 (Continued).

Drug	Study Type	Main Outcomes	Conclusions	References
Emodin	In vitro In vivo	• Accelerated healing • Enhanced ECM synthesis • Promoted M2 polarization via NF-κB inhibition	A promising agent by modulating macrophage polarization and ECM formation	[107]
Sulforaphane	In vitro In vivo	• Accelerated healing • Enhanced macrophage efferocytosis Promoted M2 polarization via Nrf2/HO-1.	A potential agent by modulating macrophage function and reducing inflammation.	[108]
Apigenin	In vitro In vivo	• Promoted M1-to-M2 polarization • Enhanced HUVEC migration and VEGF secretion.	Apigenin is a potential therapeutic agent for diabetic wounds due to its ability to modulate macrophage polarization and enhance angiogenesis	[109]
Paeonol	In vitro In vivo	• Promoted M2 polarization • Enhanced collagen deposition and angiogenesis • Reduced inflammation	Accelerates diabetic ulcer healing by modulating macrophage polarization.	[110]
Paeonol	In vitro In vivo	• Promoted M2 polarization • Reduced inflammation • Accelerated healing via DDIT4-mTOR pathway	A potential agent for DFUs by modulating macrophage polarization.	[111]
Iridoid glycoside extract of L. rotata (IGLR)	In vitro In vivo	• Promoted M2 polarization, angiogenesis, fibril formation • Suppressed early inflammation	Accelerates wound healing by modulating macrophage polarization and enhancing repair.	[112]
IGLR	In vitro In vivo	Suppressed oxidative stress and inflammation via Nrf2/COX2 axis Enhanced collagen deposition.	Accelerates diabetic wound healing by modulating oxidative stress and inflammation.	[113]
Calycosin-7-glucoside	In vitro In vivo	• Promoted M2 polarization • Increased anti-inflammatory cytokines • Reduced pro-inflammatory ones	Accelerates healing via the ROS/AMPK/STAT6 pathway, enhancing anti-inflammatory responses	[114]
Asiaticoside-NO	In vitro In vivo	• Upregulated miRNA-21-5p • Promoted HaCaT cell proliferation and migration.	Accelerates diabetic wound healing via miRNA-21-5p, offering a novel approach.	[115]

Asiaticoside-NO hydrogel	In vitro In vivo	Promoted epithelialization and angiogenesis Regulated apoptosis via Bcl-2/Bax/Caspase-3.	Accelerates healing by modulating apoptosis and angiogenesis.	[116]
Quercetin	In vivo (Rat)	• Promoted wound contraction • Modulated macrophage polarization (M1 to M2) • Inhibited inflammation.	Accelerates diabetic wound repair by modulating macrophage polarization.	[117]
Quercetin	In vivo (Rat)	Regulated PI3K-Akt signaling pathway Reduced inflammation.	Treats diabetic wounds by targeting multiple pathways, reducing inflammation.	[118]
Quercetin ointment	In vivo	• Accelerated wound closure • Modulated cytokines • Enhanced tissue regeneration.	Improves diabetic wound healing by regulating cytokines and growth factors.	[119]
Teucrium polium extract ointment	In vivo (Rat)	Accelerated wound healing, comparable to phenytoin ointment.	Teucrium polium extract ointment significantly enhances wound healing.	[120]
Teucrium polium hydroethanolic extract and Aloe vera gel	In vivo (Mouse)	• Shortened inflammatory phase • Reduced oxidative stress and inflammation • Increased collagen.	Co-administration accelerates healing by reducing inflammation and enhancing proliferation.	[121]
Curcumin cream	In vivo	• Enhanced neoangiogenesis • Increased NF-κB signaling.	Promotes angiogenesis in diabetic wound healing but has limited effects on inflammation.	[122]
Quercus infectoria gall hydroethanolic extract ointment	In vivo	• Accelerated wound healing • Reduced inflammation • Enhanced angiogenesis and antioxidant capacity.	Improves diabetic wound healing through multiple mechanisms.	[123]
Salvia officinalis essential oil (SOO) ointment	In vivo	• Accelerated wound healing • Reduced inflammation • Enhanced angiogenesis.	Promotes wound healing by regulating cytokines, growth factors, and antioxidant activity.	[124]
Salvia kronenburgii (SK) and Salvia euphratica var. euphratica (SE) ethanolic extracts	In vivo In vitro	• Accelerated wound healing • Exhibited antimicrobial and antioxidant activities.	Promote diabetic wound healing and possess strong antimicrobial and antioxidant properties.	[125]
Dill (Anethum graveolens) essential oil (DEO)	In vivo	• Reduced bacterial growth • Accelerated wound healing • Modulated apoptosis and proliferation.	Promotes MRSA-infected wound healing by enhancing collagen deposition and angiogenesis.	[126]

(*Continued*)

Table 1 (Continued).

Drug	Study Type	Main Outcomes	Conclusions	References
IGLR	In vivo	• Identified key active compounds • Increased bioavailability in wound tissues.	Key compounds in IGLR are responsible for accelerating wound healing.	[127]
Loureirin B	In vivo In vitro	• Downregulated collagen and α-SMA • Inhibited TGF-β1-induced fibrosis.	A potential agent for hypertrophic scar treatment by modulating fibrosis-related pathways.	[128]
Aloesin	In vivo (Mouse) In vitro	• Enhanced cell migration • Promoted cytokine release • Accelerated wound closure and angiogenesis.	Facilitates cutaneous wound healing through MAPK/Rho and Smad signaling pathways.	[129]
Gynura divaricata (L). DC.	In vivo In vitro	• Improved cell survival • Reduced apoptosis and ROS • Enhanced migration and angiogenesis via Nrf2.	Accelerates diabetic wound healing by mitigating oxidative stress and promoting angiogenesis.	[130]
Paeoniflorin	In vivo In vitro	• Activated Nrf2 pathway • Reduced oxidative stress • Enhanced cell proliferation and migration.	Promotes diabetic foot ulcer healing by activating Nrf2 pathway and enhancing angiogenesis.	[131]
Dracorhodin Perchlorate	In vivo (Rat)	• Reduced pro-inflammatory cytokines • Improved wound healing.	Enhances DFU healing through multiple targets and pathways.	[132]
Gynura divaricata	In vivo (Rat)	• Reduced IL-6 and TNF-α • Increased VEGFA expression.	Promotes diabetic foot wound healing by regulating multiple targets and signaling pathways.	[133]
Notoginsenoside Ft1	In vivo In vitro	• Accelerated wound healing • Promoted fibroblast proliferation • Enhanced angiogenesis.	Accelerates diabetic wound healing by promoting fibroblast proliferation and angiogenesis.	[134]
Hispolon	In vivo In vitro	• Enhanced fibroblast migration • Reduced oxidative stress • Promoted collagen synthesis.	Accelerates diabetic wound healing by mitigating oxidative stress and enhancing regeneration.	[135]
Methanolic extract of Berula angustifolia	In vivo	• Enhanced wound contraction • Increased hydroxyproline content.	Significantly promotes diabetic wound healing.	[136]
Myrtus communis berry aqueous extract gel	In vivo	• Accelerated epidermal and dermal maturation • Improved wound healing.	Effective for diabetic wound healing.	[137]

Extra virgin olive oil (EVOO) and hydroxytyrosol (HT)	In vivo In vitro	• Promoted wound closure, • Promoted collagen deposition • Reduced inflammation.	Effective in promoting diabetic wound healing.	[138]
Juglans regia L. leaf extract ointment	In vivo	• Enhanced wound closure • Promoted collagen deposition, fibroblast and blood vessel density. • Reduced inflammation	Accelerates diabetic wound healing.	[139]
Populus nigra flower buds ethanolic extract ointment	In vivo	• Promoted wound contraction • Enhanced antioxidant enzymes • Increased collagen regeneration.	Accelerates wound healing and tissue regeneration.	[140]
Crocus sativus L. (C. sativus) petal extract	In vivo In vitro	• Enhanced cell viability, migration, angiogenesis • Promoted collagen synthesis.	Accelerates diabetic wound healing and has therapeutic potential.	[141]
Lawsonia inermis (henna) hydroethanolic extract ointment	In vivo	• Enhanced wound contraction • Promoted collagen deposition • Re-epithelialization	Accelerates wound healing by reducing inflammation and promoting glucose uptake.	[142]
Paris polyphylla rhizome ointment	In vivo	• Accelerated wound closure • Enhanced collagen deposition • Reduced inflammation.	Effectively treats diabetic wounds, validating traditional claims.	[143]
Trifolium pratense (red clover) hydroethanolic extract ointment	In vivo	Enhanced collagen production, epidermis thickness, fibroblast distribution.	Promotes wound healing by modulating apoptosis and proliferation.	[144]
Kaempferol ointment	In vivo	Enhanced wound closure, hydroxyproline levels, and re-epithelialization.	Effective in treating both diabetic and nondiabetic wounds.	[145]
Satureja sahendica essential oil (SSO) ointment	In vivo	• Accelerated wound healing • Increased collagen biosynthesis.	Promotes wound healing by shortening inflammation and enhancing proliferation.	[146]
Anchusa azurea methanolic extract	In vivo	Enhanced burn wound healing, collagen deposition, antioxidant activity.	Exhibits significant wound healing, anti-inflammatory, and antioxidant properties.	[147]
Crassocephalum crepidioides hydroethanolic extract	In vivo	• Accelerated wound closure • Reduced inflammation • Promoted angiogenesis	Exhibits wound healing activity via antioxidant and anti-inflammatory effects.	[148]
Sorocea guilleminiana aqueous extract	In vivo In vitro	• Accelerated wound contraction • Increased fibroblast proliferation.	Promotes wound healing by stimulating fibroblast proliferation and collagen deposition.	[149]

(*Continued*)

Table 1 (Continued).

Drug	Study Type	Main Outcomes	Conclusions	References
Pimpinella anisum methanolic extract	In vivo	• Accelerated wound healing • Improved fibroblast proliferation.	Promotes diabetic wound healing by modulating oxidative stress and collagen synthesis.	[150]
Salvia huberi ethanolic extract ointment	In vivo	• Accelerated wound healing • Reduced oxidative stress.	Promotes diabetic wound healing by modulating oxidative stress and growth factors.	[151]
Syzygium mundagam bark methanol extract	In vivo	• Accelerated wound healing • Promoted epithelialization • Enhanced collagen formation	Effectively promotes diabetic wound healing.	[152]
Lycium depressum methanolic extract	In vivo	• Enhanced wound contraction • Reduced epithelialization time.	Improves wound healing parameters in diabetic rats.	[153]
Struthanthus vulgaris 5% ointment	In vivo	• Accelerated wound closure • Modulated inflammation • Enhanced collagen deposition.	Promotes wound healing by regulating cytokines and improving scar quality.	[154]
Hippophae rhamnoides leaf aqueous lyophilised extract	In vivo In vitro	• Accelerated wound closure • Modulated inflammation • Enhanced collagen deposition.	Promotes wound healing by regulating cytokines and improving scar quality.	[155]
Pien Tze Huang	In vivo In vitro	• Reduced ROS levels • Inhibited apoptosis • Enhanced wound closure.	Promotes diabetic wound healing by modulating fibroblast apoptosis and collagen synthesis.	[156]
ON101	Clinical trial (RCT)	Significantly higher complete healing rate (60.7%) vs control (35.1%).	Demonstrates superior efficacy for DFU treatment compared to standard dressing.	[89]
ON101	Post hoc analysis	Superior healing in high-risk patients (eg, large ulcers, high HbA1c).	An effective option for DFU patients with complex conditions.	[90]
Teucrium polium ointment	Clinical trial (RCT)	• Reduced ulcer area • Improved healing time • Increased complete recovery rates	Significantly enhances healing of non-infected DFUs.	[91]

Table 2 Comparison of Major Natural Product Categories and Delivery Systems for Diabetic Foot Ulcer Management

Therapeutic Modality		Key Mechanisms/ Characteristics	Representative Compounds	Advantages	Challenges/Limitations
Natural product categories	Flavonoids & Polyphenols	• Potent antioxidant • Anti-inflammatory • Pro-angiogenic activities.	• Quercetin • Puerarin • Resveratrol • Curcumin	Broad bioactivity, multi-targeted effects.	Often poor solubility/bioavailability; chemical instability.
	Polysaccharides	• Immunomodulation (macrophage polarization) • Wound hydration • Biocompatibility	• Astragalus Polysaccharide • Bletilla striata Polysaccharide (BSP)	• Excellent water solubility • Low toxicity • Ideal for hydrogels.	• Complex structures; vague precise targets • Large molecular size may limit penetration.
	Saponins	• Pro-angiogenic • Neuroprotective	• Ginsenoside Rg1 • Gomisin A	• High bioactivity and potency.	• Potential cytotoxicity at high doses • Complex purification.
Delivery systems	Nanocarriers (NPs, Nanogels)	• Enhanced cellular uptake • Targeted/sustained release • Protection of actives.	• Gallium-gelatin NPs • Chitosan nanogels	• Improved bioavailability • Deep tissue penetration potential.	• Scalability/manufacturing costs • Long-term toxicity uncertainty.
	Hydrogels (incl. NO-gels)	• Moist wound environment • Facile topical application • Tunable properties	• Asiaticoside-NO gel • BSP/Berberine hydrogel	• Clinical practicality • Biocompatibility • Suitable for exudating wounds.	• Limited penetration depth • Potential for rapid release.
	Nano-in- hydrogel composites	Combines advantages of both: targeted delivery from a stable, applicable scaffold.	EGCG/Fe^{3}+-SAB-GOx Hydrogel	• Synergistic functionality • Enhanced retention and efficacy.	Increased complexity of design and characterization.

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Table 3 Research Gaps, Potential Solutions, and Priority Areas for Future Investigation

Research Gap	Potential Solutions	Priority Areas
Variability in plant sourcing and extraction	• Standardization using HPLC and LC-MS • Establishment of pharmacopeial standards	• Batch-to-batch consistency • Regulatory compliance
Limited bioavailability of natural compounds	Development of nanotechnology-driven delivery systems, including nanoparticles and NO-gels	Improved drug concentrations in deep, ischemic ulcer beds
Lack of large mammal models	Conduct in vivo studies in large mammals, such as pigs	Better replication of human DFU pathophysiology
Heterogeneity in DFU characteristics	Rigorous stratification in clinical trials based on ulcer and patient factors	Identification of responsive subgroups
Long-term safety and efficacy	• Comprehensive toxicology profiles • Monitoring of drug-herb interactions and complications	Long-term outcomes assessment
Integration with advanced modalities	Combination therapy optimization, such as natural therapeutics combined with stem cell therapy	Synergistic therapeutic effects
Biomarker-driven personalization	Identification of predictive biomarkers, including transcriptomics and proteomics	Matching patients with the most effective natural therapeutics
Real-world evidence	Establishment of registries to monitor long-term effectiveness and cost-effectiveness	Diverse clinical settings; practical applicability

Clinical trial design complexity arises from DFU heterogeneity.[159] Future trials must implement rigorous stratification based on ulcer characteristics and patient factors to identify responsive subgroups, as demonstrated by ON101's efficacy in high-risk patients. Safety and long-term outcomes require meticulous assessment, including comprehensive toxicology profiles, potential drug-herb interactions, and monitoring for long-term complications.

Future Research Priorities

Future research priorities should focus on several critical areas to advance the field of natural therapeutics for DFUs. First, the development of advanced delivery systems is essential, particularly next-generation platforms that incorporate antimicrobials or debriding enzymes alongside natural active compounds to achieve synergistic therapeutic effects. Second, combination therapy optimization should be systematically evaluated, integrating natural therapeutics with standard care and advanced modalities to maximize treatment outcomes. Third, biomarker-driven personalization is crucial, as identifying predictive biomarkers will enable the matching of patients with the most effective natural therapeutics based on their unique profiles. Fourth, research should prioritize treatment-refractory ulcers, focusing on efficacy studies in patients with hard-to-heal DFUs who do not respond to conventional therapies. Fifth, the integration of "omics" technologies, such as transcriptomics, proteomics, and metabolomics, will help elucidate comprehensive mechanisms of action and uncover synergistic phytochemical combinations. Finally, generating real-world evidence through the establishment of registries is vital to monitor the long-term effectiveness, safety, and cost-effectiveness of these therapies in diverse clinical settings. Addressing these priorities will significantly enhance the translation of natural therapeutics into clinical practice and improve outcomes for patients with DFUs. Table 3.

Conclusion

In contrast to conventional approaches that primarily address symptoms or advanced standard-of-care therapies targeting single pathways, advanced natural therapeutics present a promising multi-targeted strategy for the complex pathophysiology of DFUs. This review synthesizes evidence on bioactive compounds that modulate key healing processes, with advanced delivery systems overcoming bioavailability limitations. Preclinical and early clinical trials with standardized formulations show considerable promise. However, the current clinical evidence remains limited, primarily consisting of

a few promising but small-scale studies. This underscores the critical need for larger, well-designed randomized controlled trials to robustly establish efficacy, optimal dosing, and long-term safety.

Translating this potential into practice, however, faces challenges in phytochemical standardization, delivery optimization, and the design of robust clinical trials for heterogeneity of DFU populations. Bridging there evidence gaps is essential to seize the translational opportunities, which include developing synergistic combinations and biomarker-driven personalization.

Looking ahead, the successful integration of these therapies has the potential to significantly influence future clinical guidelines, promoting personalized wound care strategies. Broader adoption could yield substantial public health benefits, including reduced healthcare costs, improved patient outcomes, and a lower burden of diabetes-related complications. Realizing this impact necessitates continued research and collaborative innovation.

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Figure was created in https://BioRender.com.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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