Review

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Review

Topical Probiotics in Diabetic Wound Healing: Emerging Therapeutic Strategies

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Abstract

Diabetic foot ulcers (DFUs) are among the most serious and costly complications of diabetes, characterised by delayed healing, frequent infections, and a high risk of recurrence. Despite advances in wound care, many current therapies fail to address the multifactorial pathophysiology of diabetic wounds, including vascular dysfunction, immune dysregulation, chronic inflammation, and microbial imbalance. In this context, topical probiotics have emerged as a promising microbiome-based strategy aimed at restoring microbial balance while promoting tissue repair. This review summarises current evidence on the use of topical probiotics in diabetic wound healing, with a particular focus on DFUs, outlining key pathophysiological barriers to healing and examining how probiotic therapies may counteract these processes through antimicrobial, antibiofilm, immunomodulatory, and pro-angiogenic mechanisms. Preclinical studies consistently report accelerated wound closure, reduced bacterial burden, modulation of inflammatory responses, and enhanced collagen deposition and angiogenesis following topical probiotic application, while early clinical studies report encouraging outcomes, including improved healing rates and favourable safety profiles. In addition, recent advances in probiotic delivery, such as bioengineered dressings, postbiotic formulations, and nano-enabled systems designed to improve stability and therapeutic effectiveness, are discussed. While existing data support the potential of topical probiotics as promising adjuncts in DFU management, larger, well-designed clinical trials and deeper mechanistic studies are still needed to define optimal formulations, confirm long-term safety, and enable successful clinical translation.

Keywords: diabetic foot ulcers; topical probiotics; wound healing; skin microbiome; biofilms; inflammation; angiogenesis

1. Introduction

Diabetes mellitus is a growing global health challenge, currently affecting more than 500 million adults, with numbers expected to rise sharply in the coming decades. Among its many complications, diabetic foot ulcers (DFUs) remain among the most disabling and costly. Around one in four people with diabetes will develop a foot ulcer during their lifetime, [1] and many of these wounds fail to heal properly. This often leads to persistent infection, repeated recurrence, and in severe cases, lower-limb amputation. Beyond the physical consequences, diabetic wounds also carry heavy psychological, social, and economic costs which further highlights the urgent need for more effective treatment strategies.

Despite advances in wound care, the clinical management of diabetic wounds remains challenging. Standard management of diabetic wounds includes pressure offloading, surgical debridement, infection control, revascularization procedures, and advanced dressings [2]. However,

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even with appropriate care, healing is frequently delayed, and ulcer recurrence remains common. This reflects the complex pathophysiology of diabetic wounds which includes cellular dysfunction, altered inflammatory responses, oxidative stress, the formation of advanced glycation end-products and neurovascular abnormalities [3]. In addition the development of antimicrobial resistance, which affects both clinical and therapeutic outcomes, with consequences ranging from treatment failures and the need for expensive and safer alternative drugs to the cost of higher rates of morbidity and mortality, longer hospitalization, and high-healthcare costs [4]. Together, these challenges underscore the critical need for new, locally acting therapies capable of addressing both the microbial and host components of impaired wound repair.

Probiotics, defined by the World Health Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host," have traditionally been studied mainly in gut health. However, recent advances have expanded their application to dermatology and wound management, particularly topical formulations delivering beneficial microbes directly to the wound bed.

While classical Lactobacillus species remain widely studied, recent research has broadened the probiotic repertoire to include commercially available strains such as Bacillus clausii (Enterogermina®), Lactobacillus sporogenes (Sporlac®), and Bifidobacterium longum (Florachamp®) formulated in biocompatible PEG–glycerol gels. These novel strains have demonstrated potent antimicrobial effects against common wound pathogens including Staphylococcus aureus and Pseudomonas aeruginosa, alongside significant enhancement of wound contraction, collagen deposition, and re-epithelialization in preclinical diabetic wound models, achieving healing efficacy comparable to standard treatments [5].

Topical probiotic therapies exhibit diverse biological activities: competition with pathogenic microbes for adhesion sites and nutrients, secretion of antimicrobial peptides and organic acids, modulation of immune responses to attenuate excessive inflammation, and stimulation of angiogenesis and tissue regeneration. Importantly, probiotic gels and dressings act locally at the wound surface, reducing systemic exposure and associated risks in vulnerable diabetic patients [6].

The aim of this review is to critically evaluate the emerging role of topical probiotics in diabetic wound healing, with particular attention to their application in diabetic foot ulcers. We summarize the key pathophysiological barriers to healing in diabetic wounds, review the available preclinical and clinical evidence on topical probiotic therapies, and discuss recent innovations, current limitations, and future directions for their translation into routine clinical practice.

2. Pathophysiology of the Diabetic Wounds

Diabetic wounds develop due to a complex interplay of metabolic, vascular, neuropathic, and immune factors. These interacting mechanisms disrupt the normal sequence of tissue repair and lock the wound into a chronic non-healing state.

Microvascular and macrovascular damage play a leading role due to impaired tissue metabolism in DM (7). Persistent hyperglycaemia induces endothelial dysfunction through activation of the polyol, hexosamine, advanced glycation end-products (AGEs), and protein kinase C (PKC) pathway [8]. Activation of these enzymes results in dysfunction of microarterioles that regulate the contractility of the smooth muscle of vessels supplying distal tissue areas [9]. This can be associated with delayed wound healing due to a restriction of oxygen and nutrient supply by impaired arteriole relaxation [10].

Oxidative stress represents a key downstream consequence of these activated biochemical pathways. Signalling through the AGE/RAGE axis, polyol pathway, PKC activation, and the hexosamine pathway leads to excessive production of inflammatory mediators and profound structural changes in the microvasculature. These include pericyte degeneration, basement membrane thickening, endothelial hyperplasia, nitric oxide reduction, impaired vasodilation, and increased levels of procoagulant biomarkers such as IL-6, TNF-α, D-dimer, and PAI-1 [11]. Collectively, these alterations drive the development of diabetic microangiopathy. Structural damage

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at the capillary and arteriolar level further compromises the delivery of oxygen, nutrients, and activated immune cells to the tissues, increasing susceptibility to infection and accelerating both the onset and progression of diabetic ulcers.

In parallel, diabetic neuropathy significantly accelerates both ulcer formation and chronicity. The loss of protective sensation due to neuropathy and diminished trophic effect by neuropeptide deficiency lead to trauma and increased pressure on the foot skin and a diminished hyperemic response to tissue injury [12]. These alterations may lead acute wounds to advance to chronic wounds with impaired healing [12]. More recently, small fiber dysfunction has been shown to be an early feature in patients with type 2 diabetes and has also been implicated in delayed wound healing [13].

Under physiological conditions, wound healing is a finely coordinated process that works to control infection, clear away damaged tissue [14] and restores homeostasis and tissue function through four phases: haemostasis, inflammation, proliferation and remodelling [15,16]. In diabetes, this orderly sequence becomes profoundly disrupted. Recruitment and proliferation of progenitor cells are impaired, growth factor release is reduced, and new vessel formation is diminished [14,17]. Macrophages, which are key regulators of tissue repair, show delay in the production of chemokines and cytokines such as MCP-1 and MIP-2, resulting in delayed monocyte influx into the wound [18]. This delay leads in defective efferocytosis [19], allowing the accumulation of wound debris, apoptotic cells, and neutrophils. The prevalence of wound debris sets up a constant inflammatory phase which degrades the wound microenvironment [19]. Inflammation persists into the remodeling stage, preventing complete resolution of wound healing [18].

In addition, neutrophil migration is slowed and macrophages efficiency is reduced, weakening host defense and increasing the vulnerability to infection. Additionally, advanced glycation end-products (AGEs) alter collagen structure, reducing tissue elasticity and repair capacity. Prolonged inflammation, impaired angiogenesis, and poor extracellular matrix remodeling contribute to the chronicity of diabetic wounds [20].

Diabetic wound environment is also exceptionally vulnerable to pathogenic colonization. Bacterial growth is promoted by hyperglycemia and tissue ischemia, while bacterial clearance is reduced by immune dysfunction. Chronic wounds are typically colonised by polymicrobial biofilms composed mainly of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and anaerobic species [21]. Biofilms are highly resistant to antibiotics and host defense and produce toxin while maintaining inflammation [22]. Within this dysregulated environment, balance between commensal and pathogenic organisms is lost, thereby reinforcing infection, tissue destruction, and delayed healing. This microbial imbalance provides a strong biological rationale for exploring probiotics as a strategy to restore microbial equilibrium and support wound repair

3. From Dysbiosis to Repair: The Therapeutic Logic of Probiotics

Healthy skin is an ecosystem composed of a diverse community of microorganisms, including bacteria, fungi, and viruses, that together form the skin microbiome [23]. In balance, these microbial residents play an important protective role: they compete with potential pathogens for nutrients and space, produce antimicrobial compounds, and help maintain an immune environment that supports tissue integrity. This symbiotic relationship between host and commensals contributes to skin resilience and normal wound repair.

In diabetic wounds, however, this equilibrium is disrupted. Persistent hyperglycaemia, impaired circulation and immune dysfunction create conditions that favor the growth of pathogenic species while reducing the abundance of protective commensals. Compared with contralateral healthy skin, the diabetic foot ulcer microbiota shows less bacterial diversity with greater levels of opportunistic pathogens [24]. Studies have shown that chronic diabetic wounds often develop polymicrobial biofilms, with opportunistic pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* dominating [21]. The synergistic cooperation between *S. aureus* and *P. aeruginosa* increases their tolerance to antibiotics, ability to form biofilms, and the secretion of virulence factors (hydrogen cyanide, exoenzyme S, exotoxin A, and pyocyanin for *P. aeruginosa*, and Panton-Valentine leukocidin

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and α hemolysin for *S. aureus*) that further damage tissue [25]. The loss of microbial diversity and the shift toward a pathogen-dominated ecosystem, commonly referred to as dysbiosis, is now recognised as a key barrier to wound healing, sustaining inflammation, delaying granulation tissue formation, and predisposing the wound to recurrent infection. Because this microbial imbalance plays such a central role in sustaining chronic inflammation and delayed healing, restoring a balanced wound microbiota has become an important therapeutic objective.

Within this complex environment of vascular impairment, neuropathy, immune dysfunction, microbial imbalance, and defective tissue repair, probiotics have therefore emerged as a promising therapeutic option by acting on both the wound microbiota and the host healing response. One of the most well-documented effects of probiotics is their ability to limit pathogen colonization by competing for adhesion sites and essential nutrients. It is known that probiotics interference with the QS signaling system by producing lactic acid, which decreases the pH of the local environment, and other anti-pathogenic molecules, such as hydrogen peroxide, reuterin, and bacteriocins. These substances are able to disrupt the most common chronic wound microbial pathogens or to inhibit their virulence [26,27].

Beyond their antimicrobial activity, probiotics play a critical role in disrupting biofilms, which represent one of the most important drivers of chronic wound persistence. An important antimicrobial mechanism involves regulation of antimicrobial peptide (AMPs) production by the host's epithelial cells, adipocytes, and mast cells, which modulate skin integrity, reduce inflammation, and prevent adhesion and biofilm development [28].

Lactobacillus plantarum is commonly used for the treatment of chronically infected wounds. In vitro studies have found that cell-free extracts of *Lactobacillus plantarum* strains inhibit bacterial growth and bacterial biofilm formation of *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* and hospital-derived skin pathogens [29]. *Lactobacillus plantarum* extracts were also found to reduce the expression of population-sensing signals and soluble virulence factors of pathogenic bacteria required for biofilm formation. However, the exact mechanism of reducing bacterial biofilm formation was not well elaborated on in this study [29]. Furthermore, cell-free supernatants derived from *Lactobacillus rhamnosus GG* were able to inhibit the formation of biofilms by *S. aureus* and *P. aeruginosa* by more than 95%, without causing resistance even after prolonged exposure [30,31].

Probiotics can also modulate the local immune response in wound healing by regulating cytokine production and influencing inflammatory cell recruitment [32]. They have been shown to increase anti-inflammatory cytokines such as IL-10 and TGF-β while reducing pro-inflammatory mediators like TNF-α, IL-6 and IL-1β depicts the extracted results and the main findings of the selected studies [33,34]. In addition, probiotics can influence macrophage polarisation, encouraging a shift from the destructive M1 phenotype toward the reparative M2 phenotype, thereby promoting resolution of inflammation. [35].

Another critical defect in diabetic wounds is impaired angiogenesis and keratinocyte migration, which delays tissue repair. Probiotic strains, including Lacticaseibacillus casei and Lactobacillus ramnosus GG (LGG), accelerate wound healing by releasing extracellular vesicles that promote the growth of new blood vessels (angiogenesis) and the formation of new skin (epithelialization). These vesicles contain factors like miR-21-5p, which they deliver to skin and endothelial cells, increasing their proliferation and migration to form new tissue [36,37]. In addition, *Bifidobacterium bifidum* has demonstrated potential in enhancing fibroblast activity and reducing bacterial burden in experimental models [38].

Together, these antimicrobial, antibiofilm, immunomodulatory and pro-angiogenic effects explain how probiotics can actively shift the chronic diabetic wound environment from a state of persistent inflammation and infection toward one that favours microbial balance, controlled inflammation, neovascularisation, collagen deposition, and epithelial regeneration.

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4. Evidence from Preclinical Studies

4.1. Animal Models of Topical Probiotics in Wound Healing

Experiments in animals provide the earliest evidence that probiotics can support the healing process. Most investigations have been performed in rodent models of diabetes or impaired healing, in which standardised excisional wounds are created and treated with probiotic product. The models allow researchers to quantify the immediate effect of probiotics on wound closure, prevention of infection, and tissue repair under controlled conditions.

Table 1. Summary of in vivo studies investigating topical probiotics in diabetic foot healing, focused on diabetic wounds. The table highlights study type, author and year, wound model, probiotic formulation, experimental model/patients, and reported in vitro activities.

Study Type	Author/Year	Wound Type / Model	Probiotic / Formulation	Application	Key Outcomes
In vivo (Rats, diabetic)	Salaran 2019	Burn wounds in diabetic rats	L. plantarum gel	Topical	Faster re-epithelialisation, infection control
In vivo (Diabetic rats)	Huang 2021	Diabetes-induced wounds	L. casei + exopolysaccharide	Topical gel, 14 d	Enhanced wound contraction
In vivo (Diabetic rats)	Chen 2021	Diabetic wounds	L. plantarum TWK10-fermented soymilk extract	Topical 14 d	↓ inflammation, ↑ collagen, angiogenesis
In vivo (Diabetic rats)	Al-Ghazzewi 2021	Diabetic burn wounds	L. plantarum gel	Topical, twice daily, 14 d	↑ collagen, fibroblasts, TGF-β; ↓ infection
In vivo (Diabetic rats)	Mohtashami 2021	Diabetes-induced wounds	L. bulgaricus, L. plantarum	Topical, 14 d	Faster closure, immune modulation
In vivo (Mice, T1D)	Nam 2021	Type 1 diabetes-induced wounds	Lactococcus chungangensis CAU 1447 lysate	Wound dressing, 7 d	↓ wound size, ↓ MPO, ↑ cytokines & growth factors
In vivo (Rats, diabetic ulcer)	Karimi 2024	Diabetic ulcer	Oleogel with L. acidophilus, L. rhamnosus, L. fermentum, L. casei	Topical oleogel	↑ granulation, collagen, angiogenesis, antibiofilm
In vivo (Mice)	Saha et al. 2023	Excision wound model	L. plantarum in nanocurcumin-loaded wound dressing	Topical dressing	Faster closure, ↓ bacterial load, ↓ TNF-α/MMP-9, ↑ VEGF, TGF-β, antioxidant enzymes, no systemic spread
In vivo (Mice, DFU)	Wang 2025	Diabetic foot ulcer model	L. reuteri hydrogel + H_2 nanoparticles	Topical hydrogel	↓ ROS, glucose scavenging, faster closure

4.2. Strains Investigated

A variety of probiotic strains have been tested in wound models:

Lactobacillus species (*L. plantarum, L. rhamnosus, L. casei, L. acidophillus, L. fermentum, L. paracasei, L. bulgaricus, L. reuteri, L. delbreuckii, L. salivarus*) are among the most frequently studied due to their known antimicrobial and immunomodulatory properties [39]. Lactobacillus species are Gram-positive, microaerophilic and non-sporulating microorganisms that modulate immune activity in the skin and mucosa and support cutaneous homeostasis [40].

 doi:10.20944/preprints202602.0804.v1

Experimental studies have also explored combinations of strains, suggesting possible synergistic effects.

4.3. Outcomes Observed

Animal studies provide important insights into how probiotics may influence the impaired healing environment of diabetic wounds. In diabetic rat burn models, topical *Lactobacillus plantarum* gels promoted faster wound closure, enhanced re-epithelialization, and helped reduce bacterial colonization [41]. Other work using *Lacticaseibacillus casei* combined with its exopolysaccharide showed improved wound contraction and accelerated closure, suggesting a role in strengthening the early repair phases [42].

Formulations enriched with *L. plantarum* fermented soymilk extracts further demonstrated anti-inflammatory activity, increased collagen deposition, and stimulated angiogenesis, pointing to both structural and vascular repair benefits [43].

Additional studies have shown that combinations of probiotic strains may provide broader benefits. For instance, *L. bulgaricus* together with *L. plantarum* supported faster wound closure and modulated immune cell responses in diabetic rats [44]. A topical lysate of *Lactococcus chungangensis* applied to type 1 diabetic mice reduced wound size, lowered neutrophil (MPO) activity, and promoted cytokine and growth factor expression [45].

More advanced delivery systems are also being explored. A probiotic oleogel containing multiple strains (*L. acidophilus, L. rhamnosus, L. fermentum,* and *L. casei*) improved granulation tissue formation, increased collagen density, stimulated angiogenesis, and disrupted biofilms in chronic diabetic ulcer models [46]. Most recently, a hydrogel combining *L. reuteri* with hydrogen-releasing nanoparticles demonstrated the ability to lower oxidative stress, scavenge excess glucose, and enhance angiogenesis, resulting in markedly faster closure of diabetic foot ulcers in mice [5].

In the *nanocurcumin + viable Lactobacillus plantarum* dressing experiment, the combined treatment significantly sped up wound closure in mice compared to controls. The dressing reduced bacterial burden in the wound bed, lowered levels of inflammatory markers (TNF-α, MMP-9), and decreased oxidative damage (lipid peroxidation) [47]. It also boosted beneficial healing signals, including VEGF, TGF-β, and antioxidant enzymes like catalase and glutathione. What's more, the study found no evidence that the probiotic migrated from the wound into internal organs, supporting its safety in a topical application [47].

Together, these preclinical findings suggest that topical probiotics can positively influence multiple aspects of diabetic wound repair: they suppress infection and biofilms, reduce oxidative and inflammatory stress, stimulate fibroblast and collagen activity, and promote angiogenesis. While promising, these results remain preliminary and require validation in well-designed human trials before translation into clinical practice.

4.4. Limitations of Preclinical Evidence

Despite promising preclinical results, current animal models inadequately capture the full complexity of human diabetic wounds, especially neuropathy and vascular complications. This translational gap underscores the urgent need for advanced models that better mimic human diabetic wound pathophysiology to improve predictive relevance for clinical outcomes

Another difficulty is the wide variety of probiotic strains and delivery systems used—from Lactobacillus in gels to experimental hydrogels—so that it is difficult to compare results or know which approaches are likely to work best.

Studies are also small, often with short follow-up periods, so we know little about long-term effects or optimal dosing.

Finally, safety has not been fully explored, and the use of live microorganisms in open diabetic wounds raises understandable concerns about infection risk. Taken together, these considerations highlight that, while preclinical findings are encouraging, rigorous human studies are essential to confirm the true therapeutic value of topical probiotics in diabetic foot ulcers.

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5. Evidence from Clinical Studies

5.1. Overview

So far, clinical research on topical probiotics in wound care is still limited, but interest is steadily growing, especially in the context of diabetic foot ulcers (DFUs). Because these wounds are difficult to treat and often resistant to conventional therapies, they have naturally become the main focus of early probiotic trials [48–50].

Most of the published evidence comes from small randomized controlled trials, pilot studies, or carefully documented case series. While modest in scale, these investigations provide early signs of how probiotics may work in real patients. Different delivery formats have been explored, including topical gels, creams, sprays, and probiotic-enriched dressings and although methods vary, the results point in the same general direction [50,51].

Across these early reports, probiotics have been linked with faster wound closure, better infection control, and healthier tissue repair. Just as importantly, they have been well tolerated, with no major safety concerns reported in DFU patients. Still, these findings remain preliminary, and larger, more rigorous trials are urgently needed to determine whether the benefits observed so far can be confirmed and translated into standard clinical practice [48,51].

5.2. Clinical Trials and Case Studies in DFUs

Table 2 brings together the clinical trials and case reports that have tested probiotics directly in DFUs.

Table 2. Summary of published clinical evidence on topical probiotics for diabetic foot ulcers, including pilot trials, randomised studies, and case reports.

Study Type	Population	Probiotic / Formulation	Application	Key Outcomes	Reference / Location
Pilot Study (Argentina, 2022)	Patients with complicated DFUs post-debridement	Lactiplantibacillus plantarum	Topical, weekly	Faster healing, improved angiogenesis, M2 macrophage polarization, reduced pathogen burden	Argentina RCT 2022 (PMID 35336209)
Clinical Trial (Taiwan, 2023)	DFU patients	Probiotic soybean-based concentrate	Topical, twice daily	83% healed within 16 weeks, reduced healing time	Yang et al. 2023 (PMID 38063295)
Pilot Study	14 diabetic + 20 non-diabetic patients with chronic infected leg ulcers	L. plantarum	Topical	↓ bacterial load, ↑ immune cells, faster healing, improved inflammatory profile	Peral et al. 2010
Case Report	83-year-old woman with diabetes	L. acidophilus NCIMB 43030, L. plantarum NCIMB 43029, S. thermophilus NCIMB 30438	Topical, 24 days	Complete wound healing, eradication of P. mirabilis and K. pneumoniae	Venosi et al. 2019

5.3. Reported Outcomes

One of the first pilot studies applied *Lactiplantibacillus plantarum* to chronically infected leg ulcers and found not only a reduction in bacterial load, but also signs of stronger immune activity and improved wound healing [49]. Building on this, a pilot trial in Argentina reported that weekly applications of *L. plantarum* after debridement helped complicated DFUs heal faster, with new blood vessel formation and a shift of immune cells toward a more reparative, healing profile [37].

 doi:10.20944/preprints202602.0804.v1

More recently, a multicenter study in Taiwan evaluated a soybean-based probiotic concentrate and reported that 83% of DFUs achieved complete closure within 16 weeks, with a significant reduction in healing time compared with standard care [51]. In addition to faster wound closure, treatment was associated with improved tissue quality and better control of local infection, supporting the clinical efficacy of topical probiotic therapy in DFU management.

Individual case reports echo these findings. In one example, a woman with a chronic diabetic ulcer experienced complete healing after treatment with a multi-strain probiotic mixture (*L. acidophilus, L. plantarum, S. thermophilus*), which also eliminated persistent infections with *Proteus mirabilis* and *Klebsiella pneumoniae* [50].

Across these reports, the pattern is clear: probiotics appear to support faster healing, healthier tissue repair, and better control of infection [49–51]. Just as importantly, all studies note that topical probiotics were safe and well-tolerated, with no serious side effects reported [49–51]. While pilot clinical studies demonstrate safety and potential efficacy, the small patient cohorts, heterogeneous probiotic strains, variable delivery methods, and limited follow-up times challenge the drawing of definitive conclusions. For this reason, larger multicenter randomized controlled trials with standardized protocols and long-term monitoring are essential to confirm clinical benefit and to define optimal probiotic formulations and dosing strategies in diabetic foot ulcer care.

5.4. Limitations of Current Clinical Data

Although the early results are encouraging, the current clinical evidence has clear limitations. Most trials enrolled only a small number of patients, making it difficult to know if the positive results would hold in larger, more diverse populations. Follow-up times were generally short, meaning we do not yet know whether the benefits of probiotics last in the long term or if ulcers are more likely to recur after treatment. There is also considerable variation in the strains used (*L. plantarum* alone, multi-strain mixes, or soybean-based formulations), as well as in the delivery method (gels, dressings, or concentrates). This heterogeneity makes direct comparison between studies challenging and prevents us from identifying the “best” probiotic approach. On top of that, most reports come from single-centre or pilot studies, with only a handful of randomised controlled trials to date. Together, these gaps underline the need for larger, multicentre studies with stronger designs before probiotics can be confidently recommended as part of standard DFU care.

6. Innovations in Probiotic Delivery

A major challenge in translating probiotics into routine diabetic wound care lies not only in proving their effectiveness, but also in how they are delivered to the wound site. Traditional gels and ointments have shown promise, but researchers are now exploring more innovative approaches designed to enhance stability, prolong activity, and maximize therapeutic benefit [5,42,47].

One promising avenue is the use of bioengineered dressings and biomaterials that incorporate live probiotics directly into wound coverings. These dressings act as both a protective barrier and a sustained-release system, keeping the bacteria viable while ensuring close contact with the wound bed. Recent studies have used hydrogels and electrospun nanofiber scaffolds to successfully embed strains such as Lactobacillus plantarum and Limosilactobacillus reuteri, demonstrating accelerated closure, better infection control, and even promotion of angiogenesis in preclinical models [5,47].

Another line of innovation focuses on postbiotics and probiotic-derived metabolites. Instead of applying live organisms, these approaches use bacterial components or secreted products—such as short-chain fatty acids, antimicrobial peptides, or cell-free supernatants—that can mimic the beneficial effects of probiotics without the risk of bacterial translocation. For example, postbiotic lysates from *Lactococcus* and *Lactobacillus* species have been shown to dampen inflammation and promote fibroblast activity in diabetic wound models [42]. Symbiotic approaches, combining probiotics and prebiotics, have shown promising synergistic antimicrobial and immune-enhancing effects, presenting a novel therapeutic frontier [52].

 doi:10.20944/preprints202602.0804.v1

Artificial intelligence-driven personalized medicine offers a future direction, using microbiome profiling and bioinformatics to tailor probiotic formulations specific to individual patient wound characteristics, potentially revolutionizing clinical outcomes in diabetic wound care [6].

Finally, researchers are exploring synergistic combinations of probiotics with other therapies. These include pairing probiotics with antibiotics to help overcome resistant infections, combining them with growth factors to boost tissue regeneration, or even integrating them into stem cell–based therapies to enhance their survival and reparative potential. Early experimental evidence suggests that such multimodal strategies may deliver stronger and more reliable healing outcomes than any single therapy alone [43].

Together, these innovations show that the field is moving beyond simple topical applications toward smarter, more sophisticated probiotic delivery systems. By improving stability and harnessing synergies, these approaches may ultimately help probiotics achieve their full therapeutic potential in diabetic wound care.

7. Discussion

Challenges and Future Research Directions

Diabetic foot ulcers represent one of the most challenging and costly complications of diabetes, with high rates of delayed healing and recurrence despite advances in current therapeutic strategies. [1,2]. Within this therapeutic gap, topical probiotics have emerged as a promising, though still experimental, approach.

Preclinical animal studies and early data suggest that topical probiotics may influence wound healing by modulating inflammation, reducing pathogenic bacterial burden, and enhancing tissue repair processes such as collagen deposition and epithelialization; however, evidence in diabetic wound models remains limited [28,39].

Early clinical studies, though modest in scale, broadly support these experimental observations. Topical application of *Lactiplantibacillus plantarum* and other probiotic formulations in DFUs have been linked to faster wound closure, improved tissue characteristics and better control of bacterial burden, without major safety concerns [48–50]. While these outcomes are encouraging, yet they must be interpreted with caution. Trials so far have involved small numbers of patients, varied strains and delivery methods, and limited follow-up, leaving important questions about durability, reproducibility, and optimal formulation unanswered [6,28].

Looking ahead, the field is moving into more innovative territory. Bioengineered dressings, postbiotic formulations, and synergistic strategies that combine probiotics with antibiotics, growth factors, or stem cells are being explored to improve stability and potency [26,32,42]. These developments highlight the versatility of probiotics and their derivatives as future therapeutic tools.

To establish topical probiotics as a mainstream therapeutic approach for diabetic wounds, several pivotal gaps must be addressed. First, safety concerns related to applying live microorganisms in chronic wounds, particularly among immunocompromised patients, require rigorous investigation and clear regulatory guidelines [6,28]. At the same time, understanding the molecular mechanisms by which probiotics modulate immune responses, disrupt biofilms, and enhance tissue repair remains incomplete, warranting deeper molecular and omics-based studies [6,32].

Furthermore, the high heterogeneity of probiotic strains and delivery systems necessitates comparative and synergy-focused research to identify the most effective therapeutic agents and delivery formulations [28,43]. Personalized medicine approaches, leveraging comprehensive wound microbiome and immune profiling, offer an opportunity to tailor probiotic interventions to the individual patient's wound environment for improved outcomes [6].

Innovative technologies such as nanoencapsulation, stimulus-responsive hydrogels, and integration of biosensors offer exciting prospects for more intelligent and targeted probiotic delivery

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[5,47]. The clinical translation of these advanced modalities will require multidisciplinary efforts and well-designed clinical trials to optimise efficacy, safety, and patient acceptability [6].

Addressing these challenges will transform topical probiotics from experimental adjuncts into validated, precision therapies that effectively mitigate the substantial burden of diabetic foot ulcers.

8. Conclusions

In summary, topical probiotics represent an important step toward more holistic, microbiome-informed management of diabetic wounds. While they cannot yet be considered part of standard care, the consistency of early findings, their safety profile, and the growing technological innovations suggest a clear path forward. With rigorous, multicenter clinical trials and thoughtful integration into existing wound care protocols, probiotics could move from promising adjuncts to established partners in the fight against diabetic foot ulcers.

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