

Enhanced Bacterial Nanocellulose Scaffolds in Diabetic Wound Healing: A Review of Pathophysiology, Current Modalities, and Advanced Tissue Engineering Strategies

Nahal Amiri ¹, Negin Khedri ¹, Zeynab Shirazi ¹, Fatemeh Samavaty ¹, and Mohammad Reza Nourani ^{2*}

1. Nanobiotechnology, Department of Chemistry, Faculty of Basic Sciences, Islamic Revolution Comprehensive University, Tehran, Iran
2. Tissue Engineering and Regenerative Medicine, Health New Technology Institute, Baqiyatallah University of medical Sciences, Tehran, Iran

*. Corresponding author: Mohammad Reza Nourani, r.nourani@yahoo.com



Nahal Amiri
MSC. Student

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Abstract

Diabetic foot ulcers (DFUs) and chronic non-healing wounds present a profound clinical challenge, driven by a complex, interconnected pathophysiology characterized by persistent inflammation, impaired angiogenesis, extracellular matrix (ECM) degradation, and dysfunctional cellular responses. Conventional treatment approaches often fail to address this hostile microenvironment. In recent years, tissue engineering and regenerative medicine have emerged as pivotal paradigms, shifting the focus toward bioactive, smart biomaterials. Among these, bacterial nanocellulose (BNC)—a highly pure exopolysaccharide synthesized by bacteria such as *Komagataeibacter xylinus*—has garnered significant attention due to its nanofibrillar network, high water-retention capacity, biocompatibility, and mechanical integrity. However, pristine BNC lacks inherent antimicrobial activity and specific cell-instructive motifs. This review comprehensively examines the molecular mechanisms underlying diabetic wound recalcitrance and systematically evaluates current and emerging therapeutic modalities. We critically analyze the structural advantages of BNC and explore state-of-the-art functionalization strategies, including composite formulation, growth factor loading, and cellular seeding. By integrating bioactive macromolecules and therapeutic cells, enhanced BNC scaffolds serve as a dynamic, synergistic platform capable of modulating the chronic wound bed and accelerating functional tissue regeneration.

Keywords:

Bacterial Nanocellulose, Diabetic Wound Healing, Tissue Engineering, Biomaterials, Drug Delivery

Introduction

Diabetes mellitus remains one of the most accelerating global health emergencies of the twenty-first century, with its prevalence projected to impact hundreds of millions of individuals worldwide. Among its numerous secondary complications, the development of chronic, non-healing lower-extremity complications—primarily presenting as diabetic foot ulcers (DFUs)—imposes a profound socioeconomic and clinical burden [1]. Approximately 19% to 34% of patients diagnosed with diabetes will develop a DFU during their lifetime [1, 2].

These chronic wounds are heavily susceptible to stubborn polymicrobial infections, frequently progressing to deep-tissue necrosis, osteomyelitis, and downstream lower-extremity amputations [1]. Beyond the physical morbidity, the five-year mortality rate for individuals undergoing a major diabetic amputation approaches 50%, a prognosis that rivals or exceeds that of several aggressive malignancies [1, 3]. The exceptional persistence of diabetic ulcers stems from a fundamental breakdown in the body's endogenous physiological repair mechanisms [4].

While cutaneous wound healing in a healthy individual is an expertly orchestrated, dynamic sequence of hemostasis, inflammation, cellular proliferation, and matrix remodeling, the diabetic microenvironment is profoundly compromised [4, 5]. Persistent systemic hyperglycemia, peripheral neuropathy, microvascular ischemia, and local biochemical abnormalities collaborate to halt the healing process [3]. The wound bed becomes trapped in a self-perpetuating, non-healing loop, rendering standard clinical treatments like active sharp debridement, systematic infection control, and passive moisture balancing insufficient for high-grade or refractory lesions [2, 7].

To bridge this therapeutic gap, the fields of biomaterial science, tissue engineering, and regenerative medicine have converged to develop active, cell-instructive platforms [5, 10]. Modern wound care has transitioned from utilizing passive "coverings" to engineering smart, three-dimensional (3D) temporary extracellular matrix (ECM) substitutes [10]. Among the natural polymers investigated, Bacterial Nanocellulose (BNC)—an exopolysaccharide bio-synthesized by non-pathogenic bacteria—has risen to prominence as an elite candidate for chronic wound applications [6, 11]. BNC exhibits a unique, highly crystalline nanofibrillar network that endows it with high mechanical strength, gas permeability, and a water-retention capacity that mimics native soft tissues [11, 12].

Despite these physical advantages, pristine BNC is biologically inert; it lacks inherent antimicrobial defense mechanisms and does not possess the specific biochemical signaling motifs required to actively stimulate local cells or trigger neovascularization [6, 11]. Consequently, contemporary research focuses on designing "enhanced" BNC platforms [11, 14]. By functionalizing the nanocellulose meshwork through the integration of complementary polymers, small-molecule phytochemicals, targeted growth factors, and therapeutic cell lines, investigators have engineered responsive, multi-targeted regenerative tools [14, 17].

This review provides a comprehensive analysis of enhanced BNC architectures within the context of diabetic cutaneous repair. We examine the molecular pathophysiology that drives diabetic wound recalcitrance, critically review the historical and emerging medical modalities, evaluate the structural attributes of BNC, and dissect modern functionalization protocols. Ultimately, we highlight how these integrated biomaterial platforms can suc-

cessfully remodel the hostile diabetic microenvironment to guide functional tissue regeneration.

Methodology

A comprehensive literature search was conducted to identify relevant studies on the application of bacterial nanocellulose in diabetic wound healing. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were systematically searched for articles published between 2010 and 2026.

The search strategy involved the use of the following keywords and their combinations: "bacterial nanocellulose", "diabetic wound healing", "diabetic foot ulcer", "wound dressing", "tissue engineering", "biomaterials", "drug delivery", and "chronic wounds".

Original research articles, review articles, systematic reviews, meta-analyses, and relevant clinical studies published in English were considered eligible for inclusion. Studies were selected based on their relevance to the role of bacterial nanocellulose in wound management, tissue regeneration, antimicrobial activity, and advanced wound dressing development.

Duplicate publications, conference abstracts without full texts, non-English articles, and studies unrelated to diabetic wound healing or bacterial nanocellulose were excluded. The selected articles were critically analyzed and synthesized to provide an up-to-date overview of current advances, challenges, and future perspectives regarding bacterial nanocellulose-based strategies for diabetic wound healing.

The reference lists of the selected articles were also manually screened to identify additional relevant publications.

1. Pathophysiology of Diabetic Wounds

Wound healing in individuals with diabetes mellitus is a highly compromised physiological process [1, 3]. In healthy tissue, wound healing progresses through four precisely orchestrated, overlapping phases: hemostasis, inflammation, proliferation, and remodeling [4, 5]. In patients with diabetes mellitus, this cascade is profoundly disrupted, arresting the wound in a chronic, non-healing inflammatory state [1, 2].

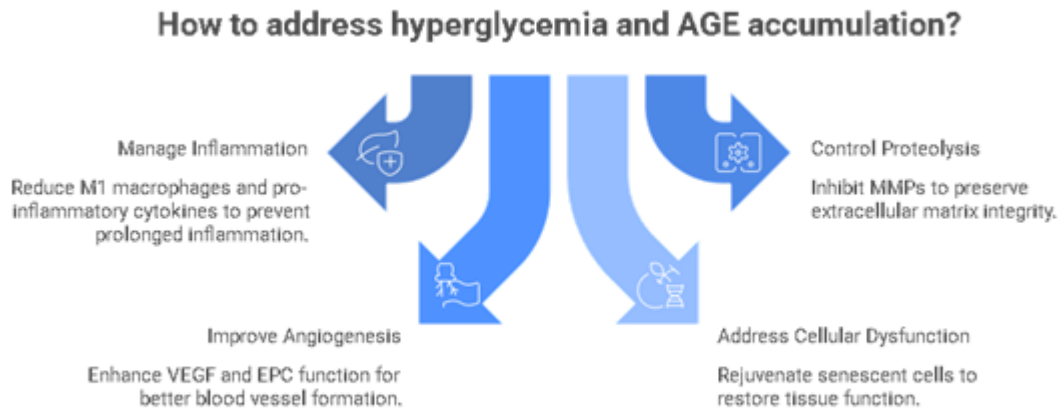


Figure 1: [Hyperglycemia / AGE Accumulation]

Sustained Inflammation and Macrophage Polarization

The diabetic wound bed is characterized by a prolonged, dysregulated inflammatory phase [2, 5]. Under normal conditions, pro-inflammatory (M1) macrophages transition to an anti-inflammatory, pro-healing (M2) phenotype to drive tissue repair [5]. In the diabetic microenvironment, persistent hyperglycemia and the accumulation of Advanced Glycation End-products (AGEs) lock macrophages into the M1 phenotype [1, 2]. This sustained polarization leads to the chronic overproduction of pro-inflammatory cytokines, including:

Tumor Necrosis Factor-alpha (TNF- α)

Interleukin-1 beta (IL-1 β)

Interleukin-6 (IL-6)

Extracellular Matrix Dysfunction and Proteolytic Imbalance

The chronic inflammatory state drives an upregulation of Matrix Metalloproteinases (MMPs), particularly MMP-2 and MMP-9 (gelatinases), alongside a concomitant downregulation of Tissue Inhibitors of Metalloproteinases (TIMPs) [3, 6]. This severe proteolytic imbalance results in the rapid degradation of newly synthesized extracellular matrix (ECM) components and essential structural proteins, such as fibronectin and native collagen type I and III [3]. Consequently, the provisional matrix required for cell migration and structural support is systematically destroyed [1].

Impaired Angiogenesis and Growth Factor Signaling

Neovascularization is crucial for delivering oxygen and nutrients to the regenerating tissue bed [1, 4]. In diabetic wounds, angiogenesis is heavily suppressed due to downstream signaling deficits [1, 2]. Hyperglycemia impairs the expression of Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor-2 (FGF-2) [3, 4]. Furthermore, the high proteolytic activity in the wound bed degrades these growth factors rapidly after secretion [2, 5]. Endothelial Progenitor Cells (EPCs) derived from the bone marrow display impaired mobilization, homing, and proliferation capabilities, resulting in microvascular insufficiency and persistent hypoxia [1, 2].

Cellular Senescence and Dysfunction

Dermal fibroblasts and keratinocytes within diabetic ulcers exhibit a senescent phenotype [3, 4]. These cells show diminished proliferative capacity, impaired migratory velocity, and a blunted response to regular biochemical cues [3]. Fibroblast collapse, secondary to broken collagen networks and reduced mechanical tension, inhibits the synthesis of procollagen, establishing a self-sustaining cycle of matrix degradation and cellular failure [4].

2. Current Treatment Approaches

Standard clinical management of diabetic wounds focuses on symptom mitigation and local wound

care, though efficacy remains limited for advanced ulcers [1, 7].

Standard Clinical Protocols

The foundational clinical protocol for diabetic wound management is summarized by the TIME acronym [7, 8]:

Tissue Debridement: Removal of necrotic, devitalized, or infected tissue to eliminate barriers to healing and reduce bacterial bioburden.

Infection Control: Utilization of systemic antibiotics or topical antimicrobials (e.g., silver sulfadiazine, iodine-based dressings) to manage microbial colonization.

Moisture Balance: Application of advanced dressings (hydrogels, alginates, hydrocolloids) to maintain a moist environment without causing peri-wound maceration.

Edge of Wound: Addressing non-advancing epidermal borders through pressure offloading and specialized compression therapies.

Conventional Pharmaceuticals

Topical pharmacological interventions seek to alter the biochemical landscape of the wound [7]. Standard agents include enzymatic debriding ointments (such as collagenase) and topical antimicrobials [8]. However, conventional pharmaceuticals face distinct limitations:

Rapid enzymatic inactivation within the protease-rich diabetic wound bed [2, 7].

Poor bioavailability and short half-life, necessitating frequent, painful dressing changes [8].

Potential cytotoxic effects of broad-spectrum antimicrobials (e.g., silver ions) on migrating keratinocytes and fibroblasts when applied at high concentrations [6].

Phytomedicines and Herbal Remedies

To circumvent the limitations of synthetics, research into plant-derived bioactive compounds has expanded significantly [6, 9].

Curcuma longa (Curcumin): Demonstrates potent antioxidant and anti-inflammatory properties by suppressing NF- κ B signaling pathways and scavenging Reactive Oxygen Species (ROS) [9].

Aloe vera: Contains acemannan, a complex polysaccharide that stimulates fibroblast proliferation and upregulates collagen synthesis [8].

Centella asiatica: Enriched in triterpenoid saponins (such as asiaticoside), which enhance the tensile strength of newly formed skin and promote angiogenesis [9].

Despite their therapeutic potential, crude plant extracts are limited by variable batch-to-batch composition, low aqueous solubility, and rapid clearance from the wound site, requiring advanced delivery systems for clinical efficacy [6, 9].

3. Novel and Emerging Treatment Modalities

To address the deep-seated pathophysiological blocks of diabetic wounds, several advanced physical and biological therapies have been introduced into specialized clinical practice [1, 7].

Hyperbaric Oxygen Therapy (HBOT)

HBOT involves placing the patient in a pressurized chamber to breathe 100% oxygen [1]. This intervention dramatically increases plasma oxygen tension, temporarily reversing the localized hypoxia characteristic of diabetic ulcers [1, 2]. At the molecular level, HBOT:

Stimulates ROS-dependent signaling pathways that upregulate VEGF expression [1].

Enhances the oxidative killing capacity of polymorphonuclear neutrophils (PMNs) against localized bacterial infections [1].

Promotes the recruitment and homing of circulating endothelial progenitor cells to the wound site [2].

Negative Pressure Wound Therapy (NPWT)

NPWT applies a controlled sub-atmospheric pressure via a sealed foam dressing [7]. This mechanical stimulus removes excessive exudate and interstitial fluid, thereby reducing localized edema and improving microvascular perfusion [7, 8]. The macro- and micro-deformation forces applied to the wound tissue stretch the extracellular matrix, mechanically triggering intracellular signaling pathways that promote cellular proliferation, migration, and granulation tissue formation [7].

Cold Atmospheric Plasma (CAP) and Photobiomodulation

CAP Therapy: Utilizes partially ionized gases to generate a precise cocktail of reactive oxygen and nitrogen species (RONS) [6]. At low doses, CAP induces a transient, beneficial oxidative stress that

Table 1: Biomaterials: Natural vs. Synthetic Scaffolds

Component	Class / Type	Key Wound-Healing Properties	Primary Limitations
Biomaterials	Natural (Collagen, Chitosan)	Biomimicry, biocompatibility, controlled degradation, tunable mechanical profiles	Natural: Batch variability, fast degradation.
	Synthetic (PLA, PLGA)		Synthetic: Acidic byproducts, lack of cell motifs.
Macromolecules	Glycosaminoglycans (HA), Alginate	High moisture retention, CD44 receptor interaction, exudate management	Lack of inherent structural stability, minimal cell adhesion without modification.
Growth Factors	recombinant human VEGF, PDGF-BB	Targeted activation of angiogenesis, fibroblast proliferation, chemotaxis	Rapid enzymatic degradation by MMPs, high cost, potential oncogenic risk at high systemic doses.
Cell-Based Therapies	MSCs, Fibroblasts	Paracrine signaling, immunomodulation, native ECM synthesis	Low survival in ischemic wound beds, complex regulatory approvals, high costs.

stimulates dermal fibroblast migration and angiopoiesis, while simultaneously exhibiting broad-spectrum antimicrobial activity through the disruption of bacterial cell walls [6].

Photobiomodulation (Low-Level Laser Therapy): Emits specific wavelengths of light (typically 600–1000 nm) absorbed by cytochrome c oxidase within the mitochondrial respiratory chain [5]. This photo-activation increases adenosine triphosphate (ATP) production, accelerates cellular metabolism, and downregulates pro-inflammatory cytokines [4, 5].

4. Regenerative Medicine and Tissue Engineering Approaches

Tissue engineering strategies aim to replace, repair, or regenerate damaged diabetic dermal matrices using an integrated combination of biomaterial scaffolds, macromolecules, bioactive factors, and living cell types [5, 10].

Biomaterial scaffolds provide the temporary 3D architecture required for cell attachment, migration, and tissue ingrowth [10].

Natural Biomaterials: Scaffold options such as collagen, gelatin, silk fibroin, and chitosan offer high biocompatibility and contain endogenous cell-adhesion ligands (e.g., RGD sequences) [10]. However, they

often suffer from poor mechanical stability and variable degradation rates [10].

Synthetic Biomaterials: Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) provide highly reproducible, tunable mechanical properties and degradation kinetics [5]. Nevertheless, their degradation yields acidic byproducts that can exacerbate local inflammation, and they lack inherent biological signaling domains [5, 10].

Macromolecules and Growth Factors

The incorporation of specific macromolecules, such as Hyaluronic Acid (HA), modulates early stages of repair by binding to cell-surface receptors like CD44, promoting migration and minimizing scarring [4].

Concurrently, delivery of exogenous growth factors addresses signaling deficits in the diabetic wound bed [1, 3]:

Platelet-Derived Growth Factor (PDGF-BB): Stimulates the recruitment and proliferation of fibroblasts [3].

Vascular Endothelial Growth Factor (VEGF): Directly drives the sprouting of new capillaries [1].

To be effective, these factors must be protected from proteolytic cleavage through encapsulation or matrix binding [5].

Cell-Based Therapies and Synergistic Combinations

The transplantation of therapeutic cells—including bone marrow or adipose-derived Mesenchymal Stem Cells (MSCs), neonatal fibroblasts, and keratinocytes—shifts the wound environment from a degenerative state to a regenerative one [10]. MSCs are highly valuable due to their immunomodulatory capacity; they secrete a potent repertoire of paracrine factors that suppress M1 macrophage activation and promote M2 polarization [10].

The integration of these four components creates a synergistic dynamic: the biomaterial scaffold protects the macromolecules and growth factors from enzymatic degradation while providing a supportive, biomimetic homeostatic niche that preserves the viability and secretory function of transplanted cells [5, 10].

5. Bacterial Cellulose (BC) as a Tissue Engineering Scaffold

Bacterial Nanocellulose (BNC) has emerged as an exceptionally capable biomaterial for chronic wound applications, presenting unique structural and physical attributes that distinguish it from plant-derived cellulose and traditional synthetic polymers [6, 11].

Biosynthesis and Structural Organization

BNC is synthesized via the extracellular upregulation of cellulose chains by specific bacterial strains, most notably *Komagataeibacter xylinus* (formerly *Gluconacetobacter xylinus*) [11, 12]. Fed with hexose sugars, these micro-organisms secrete linear β -1,4-glucan chains through specialized outer-membrane pores [11, 13]. These chains spontaneously self-assemble into microfibrils, which subsequently consolidate into ribbon-like nanofibers (typically 20–100 nm in diameter) [11, 12]. This continuous extrusion process creates a highly interlaced, three-dimensional reticular nanofibrous membrane [12, 13].

Distinct Physical and Chemical Advantages

Compared to alternative biomaterials, BNC possesses a unique suite of characteristics [11]:

High Chemical Purity: Unlike plant cellulose, BNC is synthesized completely free of contaminating structural polymers such as lignin, hemicellulose, and

pectin [11, 13]. This eliminates the need for harsh, multi-step chemical extractions that can degrade polymer integrity or leave cytotoxic chemical residues [11].

BNC Production Process

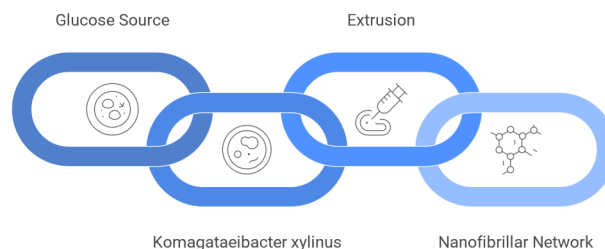


Figure 2: BNC production process: Glucose / Carbon Source *Komagataeibacter xylinus* Extrusion of β -1,4-glucan chains 3D Nanofibrillar Network (BNC)

Exceptional Water-Holding Capacity: BNC exhibits an exceptionally high degree of crystallinity (often exceeding 80–90%), yet its highly porous nanofibrillar network can retain water up to 100 times its dry weight [6, 12]. This enables efficient absorption of wound exudates while maintaining a consistently moist interface necessary for autolytic debridement [6].

High Mechanical Strength: The parallel alignment of glucan chains held together by an extensive intra- and intermolecular hydrogen-bonding network imparts remarkable tensile strength and dimensional stability to BNC sheets [11, 12]. This allows the scaffold to withstand mechanical stresses during patient movement and clinical handling [11].

Biocompatibility and Gas Permeability: BNC elicits a minimal foreign-body response when purified of bacterial cellular debris [12]. Its interconnected porosity allows for continuous oxygen and gas exchange, while establishing an effective physical barrier against secondary bacterial invasion [6, 13].

6. Bacterial Nanocellulose Applications in Wound Healing

When applied to a wound bed, pristine BNC operates primarily as a passive, high-performance protective barrier and a hydro-active dressing [10, 11].

Mechanisms of Action

The therapeutic efficacy of pristine BNC centers on its ability to optimize the physical conditions of the wound environment [6, 11]:

1. **Exudate Management and Fluid Regulation:** The capillary forces within the interconnected nanofibrous networks draw excess, destructive proteases and inflammatory exudates away from the chronic wound bed, trapping them within the matrix [6].

2. **Maintenance of a Moist Microenvironment:** BNC continuously donates moisture to dry, necrotic areas of the wound, softening eschar and accelerating natural autolytic debridement without causing maceration of the surrounding healthy skin [6, 11].

3. **Protection of Granulation Tissue:** Due to its non-adherent surface properties, BNC does not damage or tear newly formed granulation tissue or delicate, migrating epithelial sheets during dressing removal [6].

Clinical Outcomes and Limitations

Clinical evaluations of pristine BNC dressings demonstrate reduced patient pain scores, accelerated re-epithelialization rates, and fewer required dressing changes compared to conventional gauze or petroleum-impregnated dressings [6, 13].

However, pristine BNC possesses major limitations that hamper its use in diabetic wounds [6, 12]:

Lack of Antimicrobial Activity: Pristine BNC exhibits no inherent ability to kill or inhibit bacteria, rendering it vulnerable to biofilm colonization in highly susceptible diabetic ulcers [6, 12].

No Instructive Bioactivity: BNC is biologically inert; it lacks the ligands required to interact with cell-surface integrins, failing to directly stimulate or accelerate cell proliferation, migration, or angiogenesis [11, 12].

7. Enhanced Bacterial Nanocellulose Scaffolds for Diabetic Wound Healing

To transform BNC from a passive barrier into an instructive, bioactive therapeutic platform, advanced functionalization methodologies have been developed to address the specific deficits of the diabetic wound environment [11].

Incorporation of Complementary Biomaterials

Blending or forming interpenetrating polymer networks (IPNs) with other macromolecules introduces necessary biochemical cues into the BNC matrix [12]:

BNC/Chitosan Composites: Chitosan adds inherent broad-spectrum antimicrobial activity through electrostatic interactions between its positively

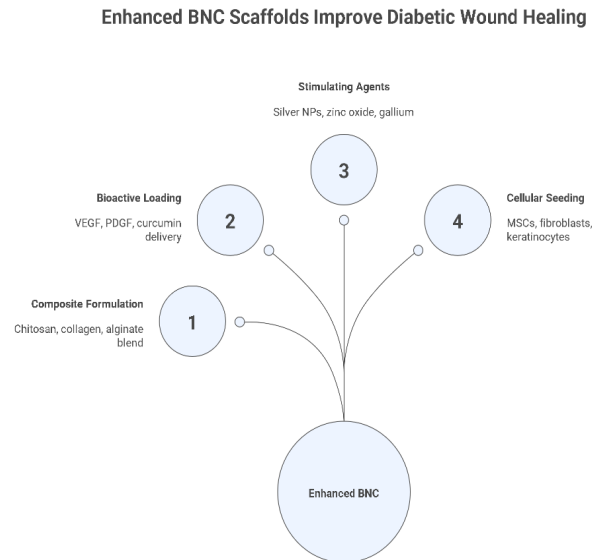


Figure 3: Enhanced BNC scaffolds improve diabetic wound healing

its positively charged amino groups and the negatively charged membranes of bacteria [11, 14].

BNC/Collagen Blends: Incorporating collagen introduces essential RGD (Arg-Gly-Asp) cell-adhesion motifs [10]. This significantly enhances the attachment, spreading, and proliferation of dermal fibroblasts and keratinocytes on the scaffold [10, 11].

BNC/Alginate Networks: Enhances the overall fluid handling capacity and structurally mimics the natural amorphous ground substance of the dermal ECM, smoothing the transition to the proliferative phase [12].

Loading with Growth Factors and Bioactive Molecules

BNC can be modified to serve as a localized drug-delivery vehicle [6]. The dense hydroxyl groups on the surface of BNC allow for the physical entrapment, ionic adsorption, or covalent conjugation of therapeutic agents [11]:

Growth Factor Delivery: Incorporating VEGF, bFGF, or PDGF-BB directly into the nanostructure allows for

sustained, localized release [11]. This localized delivery protects these fragile proteins from rapid enzymatic cleavage by MMPs, presenting them continuously to surface receptors on endothelial cells and fibroblasts to stimulate tissue regeneration [2, 10].

Phytochemical Incorporation: Loading BNC with small-molecule antioxidants such as curcumin or melatonin creates an active radical-scavenging matrix [9, 15]. This localized reduction of excessive ROS downregulates the chronic activation of pro-inflammatory transcription factors like NF- κ B [9]. Integration with Stimulating and Antimicrobial Agents

To combat the high incidence of polymicrobial biofilms in diabetic wounds, BNC scaffolds have been augmented with inorganic nanoparticles and chemical modulating agents [11, 16]:

Silver Nanoparticles (AgNPs): In situ reduction of silver nitrate within the BNC matrix generates anchored AgNPs [11, 16]. These particles release Ag^+ ions continuously, disrupting bacterial respiratory chains and cell wall integrity without inducing systemic toxicity [11, 16]

Zinc Oxide (ZnO) Nanoparticles: These metal oxides provide stable antimicrobial protection and serve as essential trace cofactors that activate endogenous tissue-remodeling enzymes [11].

Seeding with Therapeutic Cells

The highly porous structural network of modified BNC can serve as a supportive 3D architecture for cellular transplantation [10, 17]:

Mesenchymal Stem Cell (MSC) Seeding: Culturing bone marrow or adipose-derived MSCs within functionalized BNC scaffolds creates a living, responsive therapeutic system [17]. These embedded MSCs respond dynamically to the hypoxic, inflammatory signals of the diabetic wound bed by secreting an optimized mix of anti-inflammatory cytokines (IL-10, TSG-6) and pro-angiogenic factors (VEGF, Angiopoietin-1) [17].

Co-culture Systems: Simultaneously seeding the scaffold with dermal fibroblasts and keratinocytes creates a biomimetic bi-layered skin equivalent, coordinating cell-cell signaling to accelerate vascularized granulation tissue formation and rapid epidermal closure [10].

8. Recent Advances and Emerging Protocols

Recent breakthroughs in bio-fabrication and materials science have expanded the therapeutic potential of BNC scaffolds, moving away from uniform sheets toward smart, responsive systems [6, 20].

3D Bioprinting and Shape-Conformal Scaffolds

Standard BNC membranes are typically produced as flat, uniform pellicles [6, 12]. Emerging protocols utilize modified bio-inks containing short, shear-thinning BNC nanofibrils combined with alginate or photocrosslinkable hydrogels (such as GelMA) for 3D bioprinting [20]. This approach enables the automated fabrication of patient-specific, anatomically precise scaffolds [20]. By utilizing 3D wound scans, scaffolds can be printed to precisely match the irregular geometry and depth of a patient's foot ulcer, ensuring complete contact with the wound bed and optimizing cellular infiltration [20].

Stimuli-Responsive and "Smart" Dressings

Modern engineering strategies focus on developing BNC scaffolds that respond actively to changes in the wound microenvironment [6, 12]:

pH-Responsive Delivery: Chronic, infected diabetic wounds typically exhibit an alkaline pH (7.5–8.5), whereas healing wounds transition to an acidic environment [6]. BNC scaffolds modified with pH-sensitive polymers (e.g., poly(acrylic acid)) exhibit conformational changes or swelling variations triggered by these shifts, releasing antimicrobial agents or growth factors only when the wound deviates from normal healing parameters [6].

MMP-Cleavable Linkers: Covalently tethering growth factors to the BNC backbone via peptide sequences recognized specifically by MMP-9 ensures that therapeutic molecules are released in direct proportion to the severity of local inflammation, self-regulating the treatment dose [2].

9. Conclusion

The treatment of diabetic wounds requires interventions capable of correcting a severely compromised microenvironment [1, 2]. Pristine bacterial nanocellulose offers an exceptional structural foundation, providing excellent moisture management, structural integrity, and high purity [11, 12]. However, its baseline biological inertness requires advanced engineering strategies to achieve clinical success [6, 11].

By functionalizing BNC through composite formulation, antimicrobial integration, growth factor loading, and cellular seeding, researchers have converted this material into an instructive, multi-targeted regenerative matrix [10, 11]. These enhanced BNC scaffolds actively suppress chronic inflammation, eliminate bacterial biofilms, protect critical biological signals, and stimulate robust angiogenesis [11, 17].

Despite these clear preclinical successes, several key milestones must be achieved to transition these technologies to widespread clinical practice [11]:

Scaling Production and Quality Control: Developing high-throughput, cost-effective fermentation and purification protocols to eliminate all traces of bacterial endotoxins uniformly at an industrial scale [11].

Standardizing Regulatory Pathways: Navigating the complex regulatory requirements for advanced "combination products" that incorporate biomaterials, synthetic drugs, and living cellular components [10].

Long-Term Clinical Validation: Executing large-scale, multi-center randomized controlled clinical trials specifically targeting diverse diabetic patient populations to confirm long-term safety, efficacy, and cost-effectiveness relative to current standard therapies [10, 13].

Addressing these technical and clinical hurdles will position enhanced bacterial nanocellulose scaffolds as a cornerstone platform in regenerative medicine, offering a definitive clinical solution for chronic, non-healing diabetic wounds [11, 12].

Future studies should focus on translating promising preclinical findings into well-designed clinical trials to establish the safety, efficacy, and regulatory feasibility of advanced BNC-based wound dressings.

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