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Review

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Bio-enhanced silk fibroin-based scaffolds for chronic diabetic foot ulcers

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Abstract

Diabetic foot ulcers (DFUs) represent a growing clinical challenge, driven by an aging global population and the increasing prevalence of diabetes. Affecting millions worldwide, DFUs remain one of the most serious complications of diabetes, frequently progressing to infection, amputation, and elevated mortality. Standard treatments typically include pressure offloading, circulation improvement, infection control, and topical wound care; however, many chronic DFUs fail to respond to these interventions due to persistent inflammation, impaired vascularization, and microbial burden. These challenges have accelerated interest in regenerative medicine approaches, including stem cells, growth factors, and skin substitutes. Among these, skin substitutes have shown particular promise; among Food and Drug Administration-approved options, products such as the collagen-Manuka honey-hydroxyapatite patch from SweetBio (Apis®) have demonstrated improved outcomes in patients with chronic ulcers. Silk fibroin (SF), a natural biopolymer with established clinical use, has emerged as a promising platform for chronic wound management due to its biocompatibility, tunable degradation, and capacity for controlled bio-additive delivery. SF scaffolds can be fabricated through various methods tailored to wound-healing applications: electrospun fibrous mats with high surface-area-to-volume ratio, freeze-dried porous constructs with interconnected architecture, and hydrogels designed for controlled drug delivery. In this review, we critically examine how SF scaffolds enhanced with bio-additives modulate cellular responses, redirect dysregulated healing pathways, accelerate wound closure, and promote tissue regeneration in diabetic wounds. We synthesize recent advances in preclinical and clinical studies, identify key translational barriers, and outline future directions for advancing SF-based dressings toward clinical adoption. Collectively, this review positions bio-enhanced SF scaffolds as next-generation, disease-informed candidates for improving outcomes in chronic DFU care.

Keywords Diabetic foot ulcers, Chronic wound healing, Skin substitutes, Silk fibroin, Bio-additives, Scaffold fabrication, Growth factors, Tissue engineering, Regenerative medicine

Highlights

- **Chronic diabetic foot ulcers (DFUs) are driven by persistent inflammation, impaired vascularization, and microbial burden that standard care fails to resolve.**
- **Silk fibroin (SF) scaffolds (i.e. electrospun mats, freeze-dried constructs, and hydrogels) enable tunable, controlled delivery of bio-additives to dysregulated wound environments.**
- **Bio-enhanced SF scaffolds accelerate wound closure, modulate inflammatory and angiogenic pathways, and promote tissue regeneration across preclinical diabetic wound models.**
- **Clinical translation is limited by regulatory complexity, manufacturing scalability, and the lack of clinically relevant wound models; smart and responsive SF systems represent a priority direction for future work.**

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Background

Epidemiology and burden of diabetic foot ulcers

Diabetes mellitus comprises a heterogeneous group of disorders characterized by absolute or relative impairments in insulin production or action [1, 2]. As of May 2024, the United States Centers for Disease Control and Prevention estimated that 38.4 million Americans, or 11.6% of the population, are living with diabetes, while worldwide prevalence exceeds 830 million individuals [3, 4]. Global projections are even more concerning, with type II diabetes alone anticipated to affect 1.3 billion people by 2050 [5]. Type II diabetes, which accounts for 90% of all cases, is strongly linked to aging populations, increased urbanization, and obesogenic environments [6].

The systemic impact of diabetes is profound, as the disease markedly increases the risk of cardiovascular disease, peripheral vascular disease, stroke, neuropathy, renal failure, retinopathy, blindness, and limb amputations [7, 8]. Among its many complications, diabetic foot ulcers (DFUs) represent one of the most debilitating and costly. DFUs develop primarily as a consequence of peripheral neuropathy, vascular insufficiency, and repetitive mechanical trauma, affecting ∼15%–25% of individuals with diabetes and 1.6 million patients each year in the United States [9]. These open sores or wounds cause discomfort, loss of sensation, loss of motility, and reduced quality of life, while also serving as portals for soft tissue infection, gangrene, and sepsis [9].

The clinical consequences of DFUs are stark, where ∼50% of all foot ulcers become infected, 15%–20% of moderate to severe infections result in lower limb amputation, and five-year mortality approaches 30%, rising to >70% following major amputation [9–12]. Beyond the human toll, DFUs impose a significant economic burden, with direct healthcare costs in the United States alone estimated at $9–13 billion annually [13–17]. Together, these epidemiological and economic data underscore DFUs as an urgent and escalating public health challenge requiring more effective therapeutic strategies.

Challenges and limitations with current standard-of-care

The central challenge with DFUs is their development into chronic, non-healing wounds. A “controlled” wound healing response consists of four subsequent and overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Complications within the wound microenvironment caused by chronic inflammation, dysregulated angiogenesis, hypoxia-induced oxidative stress, neuropathy, advanced glycation end-products, and impaired neuropeptide signaling can all lead to chronic diabetic ulcers, which become unresponsive to standard treatment (Figure 1) [18].

As illustrated in Figure 1a, c, and e, normal wound healing follows a coordinated progression in which clot formation and an acute inflammatory response give way to angiogenesis, extracellular matrix (ECM) deposition, and tissue remodeling, ultimately restoring structural and functional integrity. By contrast, in impaired healing (Figure 1b, d, and f) wounds remain trapped in a state of prolonged and excessive inflammation, often driven by persistent neutrophil activity and damage-associated molecular patterns such as reactive oxygen species (ROS), which further exacerbate local tissue damage. Insufficient angiogenesis results in a hypoxic wound environment, impairing cell proliferation and amplifying oxidative stress. These factors collectively disrupt regeneration. Inflammatory M1 macrophages inhibit fibroblast migration and collagen deposition, while the few collagen fibers that are deposited are disorganized and mechanically weak, leaving tissue highly vulnerable to re-ulceration and infection.

Standard treatments for DFUs include patient education, blood sugar control, pressure offloading, antiplatelet agents to improve peripheral vascular circulation, antibiotics or debridement to prevent or control infection, and topical care (e.g. dressings) [7]. Wound dressings are integral to effective management of DFUs, serving both to protect the wound from bacterial invasion and to accelerate healing [19]. DFUs are commonly classified according to wound depth and the presence of necrotic tissue, most often using the Wagner-Meggitt Classification of Diabetic Foot system [7]. Importantly, not all ulcers present the same diagnosis or severity, and effective treatment must be tailored to the specific stage and characteristics of each wound. Broadly, DFUs can be categorized as either shallow or deep ulcers, with the latter carrying a substantially poorer prognosis. Deep ulcers often require surgical debridement and specialized dressings, and are far more likely to enter the impaired wound healing cascade. Once in this state, DFUs become resistant to conventional treatment and predispose patients to severe complications including infection, amputation, and even death. These high-risk wounds underscore the urgent need for innovative dressing strategies capable of modulating chronic inflammation, stimulating angiogenesis, and preventing microbial invasion—thereby actively redirecting the healing cascade toward its normal, regenerative pathway.

Advantages of silk fibroin-based scaffolds for treating non-healing DFUs

Biomaterials have emerged as promising candidates for addressing the complex macro- and micro-environmental challenges in chronic DFUs, particularly when designed to provide both structural support and biological signaling. Their inherent tunability, biocompatibility, biodegradability, and hydrophilicity, combined with the ability to be functionalized with bioactive components, make them ideal candidates to re-establish the natural healing cascade [20–24].

Among the many biomaterials explored for chronic DFU treatment, silk fibroin (SF) has emerged as a particularly promising candidate. Derived from silkworms (*Bombyx mori*), SF has a long history of medical use, most notably as suture material for centuries [25]. In more recent years, advances in processing have enabled SF to be converted into aqueous solutions and reconstituted into a variety of biomaterial formats, including sponges, films, hydrogels, electrospun mats, and even three-dimensional (3D)-printed scaffolds. This versatility, coupled with its high biocompatibility and biodegradability, has positioned SF as a valuable material for tissue engineering and wound healing applications.

In the context of wound healing, SF-based materials have demonstrated capabilities in influencing several stages of wound healing. They can modulate inflammation, stimulate angiogenesis, enhance fibroblast and keratinocyte activity, and promote

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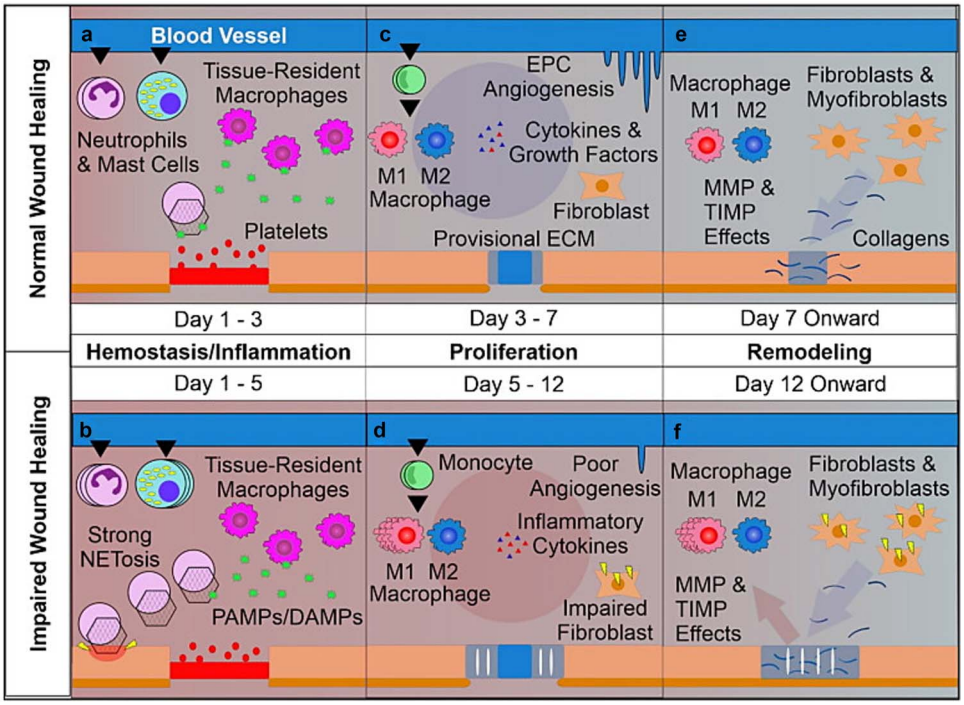


Figure 1 Normal versus impaired wound healing across the three phases. (**a**) **Hemostasis/inflammation (normal)**: platelet aggregation forms a fibronectin-rich provisional matrix while chemoattractants recruit neutrophils and mast cells, which release pro-inflammatory cytokines to clear pathogens; tissue-resident macrophages are activated. (**b**) **Hemostasis/inflammation (impaired)**: excessive neutrophil and mast cell influx sustains a hyperinflammatory state, causing collateral tissue damage and prolonging the inflammatory phase. (**c**) **Proliferation (normal)**: growth factor-driven angiogenesis restores oxygenation; infiltrating monocytes polarize into M1 and M2 macrophages, with M2-derived cytokines, growth factors, and proteases directing provisional ECM replacement with collagen, supported by functional fibroblasts, yielding granulation tissue and keratinocyte coverage. (**d**) **Proliferation (impaired)**: poor angiogenesis and glycation-induced hypoxia drive oxidative stress, skewing polarization toward M1 macrophages and impairing fibroblast function, perpetuating inflammation and inadequate ECM remodeling. (**e**) **Remodeling (normal)**: macrophages, fibroblasts, and myofibroblasts reorganize collagen via balanced MMP/TIMP activity, producing tensile, functional scar tissue. (**f**) **Remodeling (impaired)**: persistent inflammation and dysfunctional cell populations result in poor collagen reorganization, yielding mechanically weak skin prone to re-injury and ulceration. Figure obtained from Holl *et al.* [18]. *ECM* extracellular matrix

ECM remodeling. Moreover, SF dressings can be functionalized with bioactive agents such as growth factors, antimicrobial compounds, anti-inflammatories, or proteins, thereby further enhancing their therapeutic effect [26]. Evidence from *in vitro, in vivo*, and clinical studies in diabetic wound models further support these benefits. SF-based dressings have been shown to accelerate re-epithelialization, improve collagen deposition, and promote vascular regeneration, underscoring their promise as a strategy for restoring skin integrity and function in chronic DFUs (Figure 2). Taken together, these findings highlight SF as a versatile biomaterial for wound healing, particularly in chronic DFUs, where its tunable properties and capacity for biofunctionalization may help address limitations of existing dressings.

Review

Chronic wounds

Pathophysiological features of chronic DFUs

Wound healing is a highly coordinated process involving overlapping phases of hemostasis, inflammation, proliferation, and remodeling [27]. Under physiological conditions, tightly regulated cytokine signaling, controlled ECM turnover, angiogenesis, and keratinocyte migration promote timely tissue repair [27]. Disruption of these coordinated events results in impaired healing and the development of chronic wounds with diverse etiologies and underlying pathophysiological drivers, most commonly including venous stasis, pressure, diabetic, and ischemic ulcers.

Chronic wounds are characterized by prolonged inflammation, excessive protease activity, persistent oxidative stress, and microbial colonization. Elevated levels of matrix metalloproteinases (MMPs) and neutrophil elastase degrade newly formed ECM and inactivate endogenous growth factors, while sustained ROS production damages cellular components and impairs angiogenesis [28]. Additionally, bacterial biofilms contribute to immune dysregulation and antibiotic resistance, further perpetuating the inflammatory microenvironment [29].

Diabetic ulcers represent a particularly complex subset of chronic wounds, driven by systemic metabolic dysfunction rather than a localized or single-system disease process, as seen in most other forms of chronic wounds. Among these diabetic ulcers, DFUs are by far the most common form and represent a significant burden on the healthcare system at the national and global levels as discussed in the "**Background**" section (*Epidemiology and burden of diabetic foot ulcers*). In diabetes, the hallmark systemic hyperglycemia promotes the formation of advanced glycation end products, microvascular impairment, endothelial

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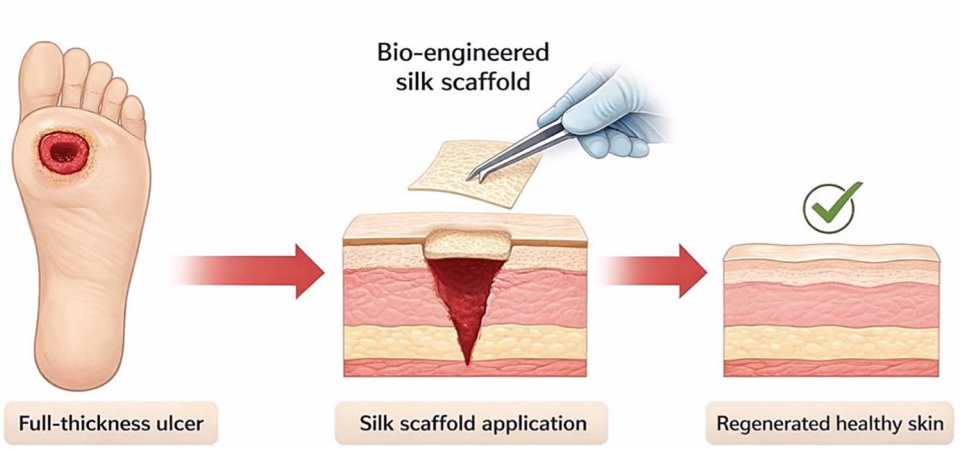


Figure 2 Clinical diagram of the potential of SF dressings for DFU treatment [created with BioRender.com]. *DFUs* diabetic foot ulcers, *SF* silk fibroin

dysfunction, and peripheral neuropathy, all of which contribute to compromised tissue perfusion and mechanical protection [30, 31]. At the cellular level, diabetic wounds exhibit persistent pro-inflammatory macrophage polarization, reduced vascular endothelial growth factor (VEGF) signaling, fibroblast senescence, impaired keratinocyte migration, and diminished collagen deposition [32–35]. Together, these abnormalities create a protease-rich, oxidative, and poorly vascularized microenvironment that actively resists endogenous repair mechanisms.

Understanding these pathophysiological features provides a clear mechanistic rationale for developing bioactive SF-based scaffolds to support healing in otherwise compromised wound environments. The material design for DFU treatment must not only provide structural support but also strategically target one or more dominant pathological domains, such as protecting therapeutic agents from degradation, modulating inflammation, reducing oxidative stress, preventing infection, and promoting angiogenesis.

Current and emerging therapies

Management of DFUs remains a major clinical challenge despite advances in wound care. Current standard-of-care treatments for deep ulcers focuses on debridement, infection control, pressure offloading, and maintaining a moist wound environment [36]. While these approaches are often effective for early-stage ulcers, they are frequently insufficient for chronic, non-healing DFUs [9, 37]. Consequently, various bioengineered and adjunctive therapies have been developed to enhance tissue regeneration and accelerate wound closure.

Several commercially available skin substitutes are Food and Drug Administration (FDA)-approved for DFU treatment, including Apis® (collagen-Manuka honey-hydroxyapatite patch) [38], Apligraf® (bi-layered collagen matrix with keratinocytes and fibroblasts) [39], and TheraSkin® (cryopreserved human split thickness allograft) [40, 41]. These constructs provide cellular and ECM support, along with native growth factors that aid in promoting granulation tissue formation and re-epithelialization toward complete wound healing. Other advanced therapies, including recombinant growth factor gels (such as Regranex® [42, 43]) and adjunctive modalities like negative pressure wound therapy or hyperbaric oxygen therapy [44, 45], have demonstrated clinical benefit in select patients but remain limited by high cost, restricted accessibility, and variable efficacy in chronic DFUs [46, 47].

Several biopolymer-based dressings (i.e. alginate, collagen, and chitosan hydrogels) have also gained FDA approval for DFU treatment due to their capacity to maintain moisture balance, regulate oxygen diffusion, and reduce microbial load [21]. Within this class, bio-enhanced SF dressings are emerging as investigational alternatives rather than established clinical standards [48]. Early pilot studies have demonstrated the therapeutic potential of bioactive SF scaffolds. For example, Chouhan *et al.* [49] examined the antimicrobial effects of LL-37 incorporated into blended SF mats, while Lin *et al.* [50] reported significantly faster wound closure using a SF film loaded with insulin-like growth factor-1 (IGF-1) compared to a conventional hydrocolloid dressing. These studies demonstrated promising safety, biocompatibility, and antibacterial activity, although large-scale randomized human trials remain limited.

Next-generation DFU therapies aim not only to achieve full wound closure but also to reactivate dysregulated healing pathways that become stalled in chronic disease. These innovations include mesenchymal (MSC) or adipose-derived (ADSC) stem cell-based therapies [51], nanoparticle and exosome delivery systems enabling localized bio-additive delivery [52], and bio-responsive "smart" dressings that modulate drug release in response to pH, temperature, or ROS within the wound microenvironment [53].

Within this regenerative landscape, SF has become a leading biomaterial platform. Its molecular structure enables tunable degradation, strong mechanical integrity, and robust functionalization with bioactive additives. Recent preclinical studies show that SF scaffolds enhanced with growth factors [e.g. epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), IGF-1], antimicrobial peptides, herbal extracts, or antioxidants significantly improve angiogenesis, collagen maturation, bacterial control, and overall wound healing in diabetic models. Electrospun SF nanofibrous mats [26], hydrogels [54], and porous sponges [55, 56] create biomimetic architectures that support fibroblast proliferation and re-epithelialization while preventing microbial invasion. Collectively, these approaches reflect a paradigm shift from passive wound coverage toward active, biomaterial-guided regeneration.

Despite encouraging outcomes, most SF-based strategies remain in preclinical or early translational stages, challenged

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by manufacturing scale-up, sterilization, processing, cost, and regulatory classification [26]. Continued development of multifunctional SF scaffolds that deliver controlled therapeutic cues while accurately mimicking ECM architecture represents a critical and promising direction for future treatment of chronic DFUs.

The source, structure, and fabrication of SF scaffolds

Types and general structure of SF

SF has become a widely studied natural biomaterial due to its biocompatibility, mechanical strength, and tunable degradation profile. Although traditionally associated with textile production, SF's unique molecular architecture and protein composition make it well-suited for biomedical applications, including wound healing and tissue regeneration.

Silk is produced by a variety of organisms (e.g. silkworms and spiders); however, this review focuses on SF derived from silkworms. Silkworm silk is typically divided into two types: mulberry, derived from the domesticated *Bombyx mori*, and non-mulberry, obtained from wild species such as *Antheraea mylitta* (Tasar), *Antheraea assama* (Muga), and *Samia ricini* (Eri) [26]. These silks differ in their fibroin composition, which influences their mechanical strength, degradation rate, and biocompatibility [57, 58]. Given its favorable properties, silk has received FDA approval for specific medical applications, underscoring its safety and versatility as a biomaterial [59].

Silk from the domesticated silkworm *(Bombyx mori*) consists of two primary proteins: an inner core of SF (70%) and an outer coating of sericin (30%), a hydrophilic protein that functions as a glue-like adhesive [60]. For biomedical applications, sericin is typically removed due to its immunogenicity, leaving SF as the principal structural protein of interest.

SF is a high-molecular-weight protein complex composed of a $\sim$ 350 kDa heavy chain and a 25 kDa light chain [60], linked by a disulfide bond between Cys-c20 of the heavy chain and Cys-172 of the light chain [61]. Proper assembly and secretion of fibroin depend on this disulfide bond that forms between the heavy and light chains; without it, silk production is severely disrupted. In fact, in a mutant silkworm lacking this disulfide bond, the resulting cocoon contained $<$0.3% fibroin [62]. This structure is further stabilized by a 25 kDa glycoprotein, P25, which associates non-covalently to ensure stability during fiber formation [61].

The primary sequence of SF is rich in glycine (43%), alanine (30%), and serine (12%). These amino acid sequences in the heavy-chain are organized into alternating hydrophobic and hydrophilic segments, producing repeating motifs such as GAGAGS and GAGAGY [60, 63, 64]. These ordered domains are interspersed with less structured segments, $\sim$42–44 amino acids long, and a 25-residue section not found in the more crystalline areas, creating a block-copolymer-like architecture that facilitates both elasticity and tensile strength, essential for the integrity of silk fibers.

SF can adopt multiple structural conformations depending on processing conditions and environmental factors. In the native state within the silk gland, fibroin exists in a water-soluble silk I conformation. During fiber spinning or after exposure to lab-prepared agents (e.g. methanol or potassium chloride), the protein undergoes a conformational shift into silk II, a stable, water-insoluble structure rich in anti-parallel β-sheets. These β-sheets are densely packed and stabilized through hydrogen bonding and van der Waals forces, conferring high mechanical strength and resistance to degradation (Figure 3) [60, 65, 66].

Bio-functional significance of SF structure

A defining feature of SF is its intrinsic ability to stabilize and protect incorporated bioactive components. This protective effect arises from the hierarchical structure of SF, characterized by alternating hydrophobic crystalline β-sheet domains and hydrophilic amorphous regions [59]. Upon β-sheet formation, the tightly packed crystalline domains create a physically crosslinked network that restricts molecular mobility and limits water penetration, thereby shielding encapsulated proteins, peptides, and small molecules from denaturation and enzymatic degradation [67, 68].

Hydrophobic interactions and hydrogen bonding between SF chains further contribute to structural rigidity [25, 69], while the mild aqueous processing conditions used in SF scaffold fabrication preserve the native conformation of sensitive biomolecules [70]. Additionally, physical entrapment within the nanofibrillar matrix reduces exposure to external proteases and oxidative stress [70, 71]. This combination of structural confinement and limited diffusion enables SF to prolong the biological activity of growth factors, antimicrobial agents, and anti-inflammatory compounds, particularly in hostile microenvironments such as chronic wounds [72].

Importantly, the degree of β-sheet crystallinity can be tuned during processing, enabling modulation of scaffold degradation rate and therapeutic release kinetics [73–75]. This tunability is particularly relevant in chronic DFUs, where the metabolically dysregulated microenvironment may alter scaffold degradation dynamics and therapeutic durability. Although SF can be engineered to degrade over weeks to months, most diabetic wound studies report only short-term follow-up and do not track scaffold resorption relative to the slower regeneration timeline characteristic of ischemic or neuropathic ulcers [48, 76–78]. Accordingly, alignment between SF degradation and long-term DFU healing remains insufficiently characterized in clinically relevant models [26, 76, 79]. Existing *in vivo* work suggests that SF supports tissue regeneration with minimal chronic inflammation, scarring, and fibrotic encapsulation; however, long-term biosafety data—particularly recurrence rates, immunogenicity, systemic exposure to degradation fragments, scarring, and functional restoration—remain limited and require further investigation [48, 80].

SF extraction

The extraction of SF from *Bombyx mori* cocoons is a multistep process designed to remove sericin and yield a purified fibroin solution suitable for biomedical applications. Degumming typically involves boiling cocoons in sodium carbonate (Na_2CO_3) for a defined duration, followed by extensive rinsing to remove sericin [59]. The degummed fibers are then dissolved [commonly using 9.3 M lithium bromide (LiBr) at elevated temperature] and dialyzed against deionized water to remove salts and obtain an aqueous SF solution. Additional clarification steps (e.g. centrifugation) may be used to remove particulates prior to downstream processing (Figure 4) [81].

For long-term storage, aqueous SF solutions may be frozen and/or lyophilized to yield a stable powder that can be reconstituted in appropriate solvents depending on the intended

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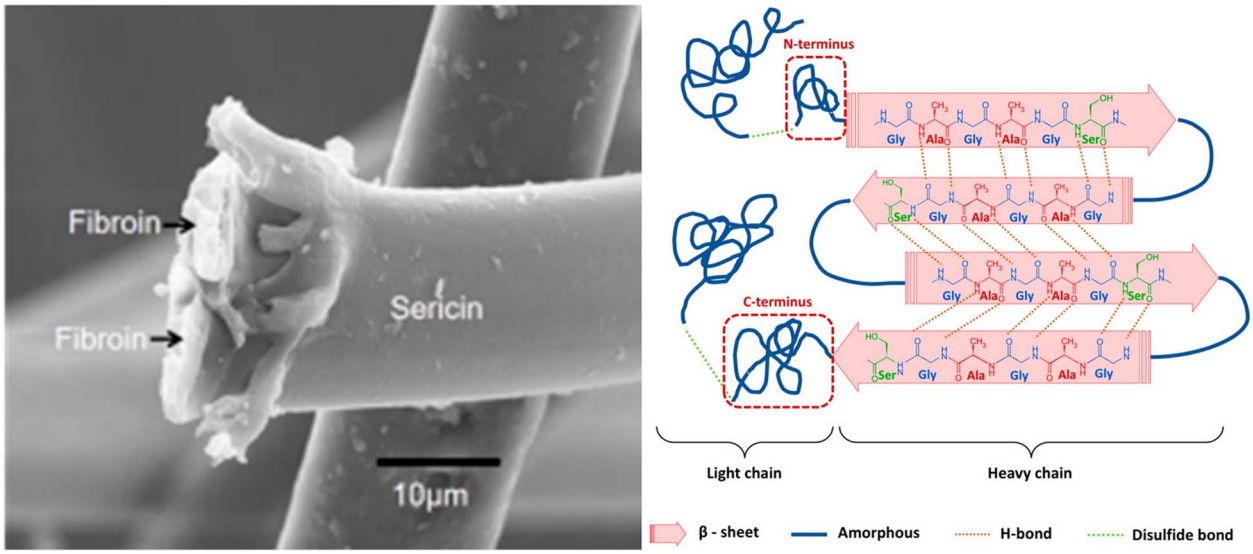


Figure 3 Silk proteins and chemical structure of SF. Adapted from Yankov *et al.* [65] and Ma *et al.* [66]. *SF* silk fibroin

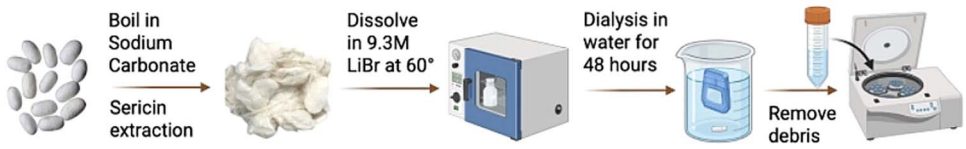


Figure 4 Schematic representation of SF extraction from *Bombyx mori* cocoons. The process includes degumming to remove sericin, dissolution in LiBr, dialysis, and reconstitution into aqueous SF solution [created with BioRender.com]. *SF* silk fibroin

application [81, 82]. This versatile extraction process enables SF to be reconstituted into a variety of scaffold formats. In the context of wound healing and DFUs, SF solutions are commonly processed into electrospun mats, hydrogels, and 3D porous scaffolds (e.g. sponges), which support bioactive loading and controlled release of therapeutic agents.

Silk fibroin-based scaffold fabrication methods

SF can be fabricated into diverse scaffold formats with tunable mechanical, structural, and biological properties. The fabrication method strongly influences scaffold porosity, degradation rate, and bioactivity, which can determine suitability for chronic wound healing applications such as DFUs. The most commonly employed approaches include electrospinning, hydrogel formation, and porous sponge fabrication (Figure 5).

Electrospun mats The skin is a multilayered organ composed of the epidermis, dermis, and hypodermis, with respective thicknesses ranging from ∼0.03–2 mm, 1–4 mm, and 0.5–30 mm [83, 84]. Electrospinning enables the creation of nanometer- to millimeter-scale fibrous mats, capable of structurally and functionally replicating these layers. Because electrospun scaffolds closely mimic the native ECM, they have gained particular attention for skin wound healing applications [85].

Briefly, electrospinning involves the dissolution of a polymer (such as SF) in a volatile solvent which is subsequently loaded into a syringe. Under high voltage, the polymeric solution is extruded toward a grounded collector at a desired speed (flow rate). The electric field induces the formation of continuous polymeric nanofibers across the working distance between the needle and a grounded target, which deposit as a nonwoven mesh [85]. These resulting nanofibrous mats possess high surface-area-to-volume ratios, tunable porosity, and pore interconnectivity, all of which facilitate nutrient, gas, and waste exchange, providing an ideal environment for cell attachment, infiltration, and proliferation [85–87].

This fabrication technique is highly versatile, as parameters such as voltage, flow rate, solvent composition, or collector design can be tuned to precisely control fiber diameter, orientation and overall scaffold architecture. In the context of chronic DFUs, electrospun SF scaffolds offer high surface area that enhances fibroblast and keratinocyte attachment, migration, and proliferation—essential processes in wound healing. The scaffold's chemical versatility also allows for incorporation (loading) of bioactive molecules such as growth factors, antimicrobials, and anti-inflammatory compounds, further enhancing their therapeutic potential [88, 89].

Hydrogels Hydrogels are 3D, water-rich, crosslinked polymer networks capable of extensive swelling in aqueous environments [89]. These scaffold types are highly valued in wound-healing applications for their ability to maintain a moist environment, absorb exudate, and enable sustained delivery of therapeutic agents. Specifically, SF hydrogels offer a unique combination of biocompatibility, tunable mechanical properties, and controllable degradation, making them excellent candidates for treating chronic DFUs. SF hydrogels can be fabricated using manual or automated techniques depending on the desired structure and function. Traditionally, SF hydrogels are formed manually by preparing an aqueous silk solution and inducing gelation through

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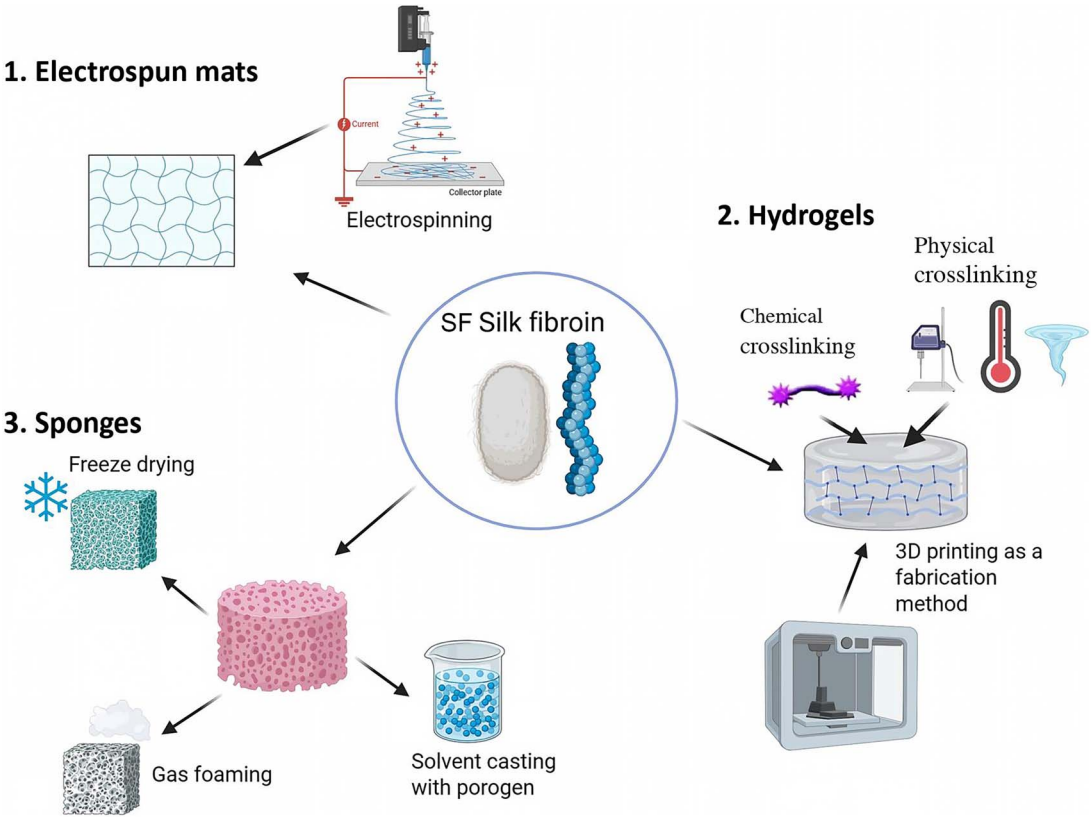


Figure 5 SF scaffold fabrication methods and final scaffold forms for application in DFU treatment [created with BioRender.com]. *DFUs* diabetic foot ulcers, SF silk fibroin

crosslinking. For more complex architectures, 3D bioprinting has emerged as a promising fabrication method. In this approach, the SF solution is combined with other biomaterials to create printable bioinks that are extruded layer-by-layer to build customized structures with controlled geometry and porosity, enhancing precision and reproducibility. Crosslinking of SF hydrogels can occur physically or chemically, both of which induce a transition from the random coiled (silk I) structure to a silk II β-sheet conformation [90].

Physical crosslinking involves non-covalent interactions such as hydrogen bonding, hydrophobic interaction, or electrostatic attraction. Techniques to achieve physical crosslinking include pH adjustment, sonication, vortexing, exposure to electric fields, and photo-crosslinking [91, 92]. In 3D printing, shear-induced gelation, pH adjustment, or temperature changes can initiate physical crosslinking within or immediately at the nozzle tip [93–95]. This allows the printed filament to retain its shape and stack into stable 3D constructs. Although physical crosslinking methods are simple and cytocompatible, they often yield hydrogels with limited mechanical strength and poorly controlled porosity [89, 96].

In comparison, chemical crosslinking allows for greater control over porosity, swelling, mechanical strength, and biodegradability. Functional groups within SF (–OH, $–NH_2$, and –COOH) can react with chemical crosslinkers to form covalent bonds and stable networks [89]. However, some chemical agents have been associated with cytotoxicity, prompting increasing use of enzymatic systems such as horseradish peroxidase (HRP) with hydrogen peroxide [97, 98]. In 3D printing, chemical crosslinking may occur either during extrusion (co-extrusion) or after printing, where incubation with the crosslinker allows precise control over gelation kinetics and final mechanical properties [98].

Ultimately, hydrogel performance depends on the interplay of gelation kinetics, pore size, and stiffness. These parameters collectively regulate drug release, nutrient diffusion, and cellular infiltration—key factors for chronic wound repair. While gelation kinetics largely governs therapeutic release profiles, pore size and mechanical properties influence cell infiltration and migration as well as structural support within the scaffold [99]. Physical crosslinking methods minimize cytotoxicity but offer less structural control, whereas chemical or enzymatic crosslinking can produce elastic, porous networks that support tissue ingrowth and angiogenesis [100–102]. Together, these properties make SF hydrogels a versatile platform for advanced dressings and localized therapeutic delivery in DFU treatment.

Sponges Porous SF sponges can be fabricated through several techniques such as solvent casting with porogens, freeze-drying, or gas foaming. These approaches produce 3D scaffolds with tunable pore size, high porosity, and interconnected networks containing features essential for nutrient exchange, cell infiltration, and tissue regeneration [55, 56].

Solvent casting with porogens involves dissolving SF in a volatile organic solvent to form a uniform solution, into which water-soluble particles are dispersed as porogens. The mixture is cast into molds to form the desired scaffold geometry and, after solvent evaporation, the construct is immersed in a solvent that selectively dissolves the porogens without affecting the polymer matrix. The leaching of porogens leaves behind interconnected

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pores, producing a highly porous structure suitable for cell growth and vascularization [56, 103].

Freeze-drying or lyophilization is among the most widely used methods for fabricating 3D porous SF scaffolds. The process begins by preparing an aqueous SF solution, which is then poured into a mold and frozen at ultra-low temperatures. During freezing, ice crystals form throughout the solution, serving as a template for the pore structure. Subsequent sublimation under reduced pressure removes ice directly as vapor, preserving the porous microstructure created by the ice crystals. Pore size and distribution can be finely tuned by adjusting parameters such as freezing rate, silk concentration, and freezing temperature, allowing optimization for cell infiltration and mechanical performance [104].

Lastly, gas foaming fabricates 3D porous scaffolds without the use of organic solvents. In this method, the polymer is first compressed into a solid form (e.g. disc or film) and then exposed to a high-pressure gas, commonly carbon dioxide [105]. Under high pressure, the gas diffuses into the polymer matrix and, upon rapid depressurization, nucleates bubbles that form pores within the material. Although gas foaming produces high porosity while avoiding cytotoxic solvents, it often yields closed pores with limited interconnectivity, which may restrict nutrient diffusion and cell migration/infiltration [106, 107]. Nevertheless, gas foaming remains a valuable strategy when solvent-free processing is desired.

Each fabrication method offers distinct advantages in controlling pore morphology, mechanical properties, and biocompatibility. For chronic DFU treatment, freeze-dried SF sponges are especially advantageous because of their highly interconnected pore networks and ability to incorporate bioactive molecules, providing both structural support and controlled therapeutic release for enhanced wound healing.

Multifunctional applications and efficacy of SF scaffolds

Bio-additives for enhancing SF scaffolds in chronic DFUs treatment

Impaired healing in DFU remains a critical clinical challenge. While the scaffold formats described above provide essential structural and physical support, the hostile microenvironment of chronic DFUs, characterized by persistent inflammation, oxidative stress, and bacterial colonization, often exceeds what SF alone can address. SF scaffolds have therefore been increasingly functionalized with bio-additives that provide targeted biochemical and biological cues to redirect dysregulated healing pathways. Building on the DFU pathophysiology and SF scaffold design principles outlined previously, we highlight representative studies demonstrating how specific additive classes—including growth factors, antimicrobial agents, anti-inflammatory compounds, cells, ECM proteins, mimetic peptides, herbal medicines, and genetic modification—enhance SF-based scaffolds for DFU treatment.

Growth factors DFUs are characterized by poor microcirculation, which limits endogenous growth-factor delivery to the wound bed [33]. Moreover, most growth factors have short half-lives *in vivo*, necessitating sustained, localized release for effective therapy [108, 109]. Controlled delivery from SF scaffolds offers a strategy to address both limited bioavailability and rapid degradation of exogenously administered growth factors [110].

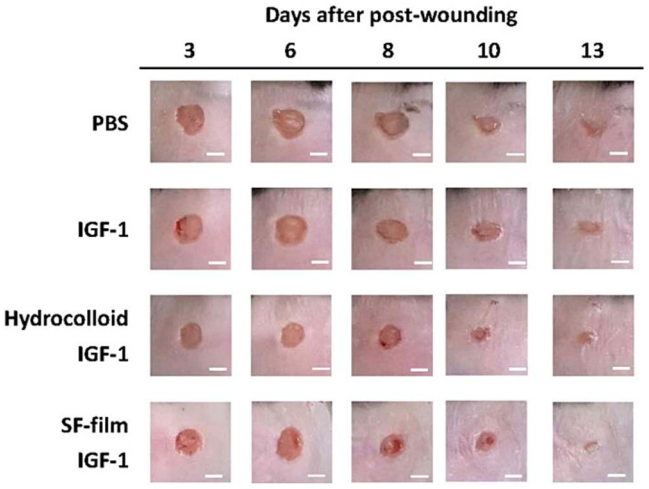


Figure 6 Wound closure over 13 days in diabetic mice treated with phosphate buffered saline (PBS; control), native IGF-1, commercial dressing product (hydrocolloid), and IGF-1-loaded SF film. Scale bars: 5 mm. Adapted from Lin *et al.* [50]. *IGF-1* insulin-like growth factor-1, *SF* silk fibroin

Lin *et al.* [50] demonstrated sustained release of IGF-1 from SF films for >30 days at 37°C. In a diabetic-mouse model, IGF-1-loaded SF films significantly accelerated wound closure compared with a commercial hydrocolloid dressing, producing smoother wound surfaces, enhanced granulation tissue formation, and increased angiogenesis (Figure 6). The authors further reported altered IGF-1 receptor signaling consistent with enhanced cell migration and proliferation, suggesting that sustained IGF-1 presentation from the SF matrix contributed to improved healing outcomes.

In a different study by Sen *et al.* [111], EGF was loaded into polyurethane (PU)/SF scaffolds and achieved complete wound healing by Day 16 with reduced microbial load. ECM analysis showed elevated glycosaminoglycan and collagen expression, while markers such as E-cadherin and MMP-9 confirmed improved cell-matrix interactions. Chouhan *et al.* [49] further enhanced electrospun SF/poly(vinyl alcohol) (PVA) mats by functionalizing them with EGF, bFGF, and antimicrobial peptide LL-37. These multifunctional scaffolds achieved ~85%–90% wound closure by Day 14 in diabetic models, with increased expression of collagen types I and III, elastin, and matrix-remodeling enzymes, as well as higher wound-breaking strength (a measure of healed tissue tensile strength) compared with controls. Importantly, this study illustrates how SF-based matrices can support the concurrent delivery of multiple growth factors while maintaining scaffold integrity and mechanical performance.

Collectively, these studies demonstrate that SF scaffolds can act as effective delivery vehicles for growth factors by stabilizing labile proteins and enabling sustained local release in diabetic wound environments. However, despite encouraging preclinical outcomes, growth factor-based SF dressings remain limited by high production cost, short intrinsic bioactivity windows, and potential safety concerns related to supraphysiologic dosing and off-target angiogenesis. These limitations underscore the importance of dose optimization, controlled release kinetics, and careful patient selection when considering growth factor incorporation into SF scaffolds for DFU treatment.

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Antimicrobial agents Bacterial colonization and biofilm formation are major impediments to DFU healing due to the hyperglycemic environment [112]. The chronic DFU microenvironment promotes persistent infection, impaired immune clearance, and biofilm formation, all of which delay re-epithelialization and granulation tissue formation. Therefore, incorporation of antimicrobial agents into SF scaffolds effectively mitigates infection while supporting regeneration.

In the study by Chouhan *et al.* [49], electrospun SF/PVA mats functionalized with the antimicrobial peptide LL-37 inhibited *Pseudomonas aeruginosa* and *Staphylococcus* growth and biofilm development. Treated wounds contained fewer than 100 bacterial colonies by Day 5, compared with >500 colonies in control wounds. This reduction in bacterial burden demonstrated the ability of LL-37-functionalized SF scaffolds to suppress infection under diabetic conditions while maintaining compatibility with wound healing processes. Khan and colleagues [113] also blended electrospun SF with zinc oxide (ZnO) nanoparticles to produce nanofibrous membranes exhibiting both antimicrobial activity and enhanced angiogenesis and collagen deposition. The SF/ZnO nanofiber composites provided a favorable microenvironment for tissue repair, supporting wound healing despite the hostile diabetic milieu. Kandhasamy *et al.* [114] further incorporated the antibacterial vitamin K3-carnosine peptide into electrospun SF fibers to address delayed tissue repair and elevated infection risk in diabetic wounds. The resulting SF nano-scaffolds exhibited potent antibacterial activity and significantly enhanced re-epithelialization and granulation tissue formation in diabetic models.

Lastly, Nanordica, a single-use antimicrobial dressing with a wound-contact layer composed of natural silk nanofibers, is currently enrolling 170 patients in a Phase I/II clinical trial for the treatment of DFUs [115]. Its antibacterial platform is based on a synergistic interaction between silver and copper nanoparticles designed to enhance broad-spectrum antimicrobial activity [116, 117]. In a 2023 *in vivo* study, the dressing demonstrated efficacy against a wide range of antibiotic-resistant bacteria [117]. In infected rat wound models, it achieved 26-fold greater bacterial inactivation than placebo dressings and a 7.6-fold greater reduction than AQUACEL® Ag Extra, a commercially available antimicrobial dressing [117]. Histological analysis further revealed enhanced re-epithelialization, reduced inflammation, and more mature collagen deposition at the wound site [117].

Together, these studies highlight the capacity of SF-based scaffolds to serve as localized antimicrobial delivery platforms that reduce bacterial burden while preserving a regenerative wound environment. However, antimicrobial incorporation introduces important translational considerations, including the risk of antimicrobial resistance, dose-dependent cytotoxicity to keratinocytes and fibroblasts, and potential disruption of commensal wound microbiota. Nanoparticle-based incorporation strategies, such as those employed in the Nanordica platform, may help modulate ion-release kinetics while mitigating antimicrobial resistance and cytotoxicity. Accordingly, antimicrobial-loaded SF scaffolds may be most appropriate for infected or heavily colonized DFUs and should be carefully designed to balance bactericidal efficacy with host-cell compatibility.

Anti-inflammatory molecules or antioxidants Persistent inflammation and oxidative stress are hallmarks of the microenvironment of chronic DFUs [118]. Excessive ROS and prolonged inflammatory signaling impair fibroblast function, angiogenesis, and re-epithelialization, contributing to stalled wound healing. To counteract these, anti-inflammatory and antioxidant compounds have been integrated into SF scaffolds. Agarwal *et al.* [119] loaded curcumin into SF-PVA or SF-polycaprolactone (PCL) electrospun scaffolds. Curcumin is a naturally occurring phenolic compound with a wide range of natural therapeutic activity including antioxidant, anti-inflammatory, and reported anti-cancer properties, as well as potential benefits in diabetic wound healing [120]. When incorporated into SF-based electrospun matrices, curcumin exhibited improved stability and sustained release relative to free curcumin formulations. The resulting scaffolds reduced inflammation and edema while promoting more organized tissue architecture and accelerated wound closure in diabetic models.

A team led by Liu *et al.* [121] explored the effects of combining SF with gelatin microspheres as a carrier for neurotensin, a neuropeptide with potent anti-inflammatory and immunomodulatory activity, to create a wound dressing for the treatment of chronic DFUs. Neurotensin is a bioactive neuropeptide that acts on mast cells, macrophages and other immune cells to stimulate cytokine release and chemotaxis, processes essential for balanced immune regulation during healing [122, 123]. The SF-neurotensin-gelatin microsphere scaffold achieved faster wound closure with minimal scarring compared with control treatments. The authors attributed these outcomes to sustained neurotensin release, efficient exudate absorption, and promotion of endothelial cell and fibroblast proliferation.

Islam *et al.* [54] developed a ROS-scavenging hydrogel by incorporating gallic acid-functionalized dendrimers into an SF-PVA network crosslinked via gamma radiation. In diabetic rat wound models, the functionalized hydrogel reduced hydrogen peroxide levels by ∼70% within 24 hours and demonstrated significantly greater hydroxyl radical scavenging compared with SF/PVA controls. *In vitro* intracellular ROS levels also decreased, indicating effective mitigation of oxidative stress. These effects were associated with faster wound closure, enhanced re-epithelialization, and improved granulation tissue maturation, suggesting that controlled ROS modulation can accelerate healing in diabetic wounds (Figure 7).

Collectively, these studies demonstrate that anti-inflammatory and antioxidant bio-additives can mitigate excessive oxidative stress and chronic inflammation when delivered via SF scaffolds. However, ROS also play essential roles in early host defense and cell signaling, where excessive or prolonged suppression may interfere with physiological repair processes. Accordingly, antioxidant-enriched SF scaffolds are likely best suited for later-stage or hyper-inflammatory DFUs, where inflammatory signaling and oxidative stress dominate over antimicrobial needs.

Cells Cells, particularly stem cells such as MSCs, are gaining substantial attention as bio-additives in advanced wound care strategies. Adipose-derived MSCs (ADMSCs) are abundant, easy to isolate, and capable of differentiating into multiple skin-related cells [124]. Beyond direct differentiation, MSCs contribute to wound repair primarily through paracrine signaling, including the secretion of pro-angiogenic, immunomodulatory, and pro-regenerative factors. When integrated into SF scaffolds, cellularized constructs can enhance angiogenesis, ECM deposition, and overall tissue regeneration. However, clinical translation remains challenged by potential immune responses to allogeneic cells, scalability, and regulatory considerations.

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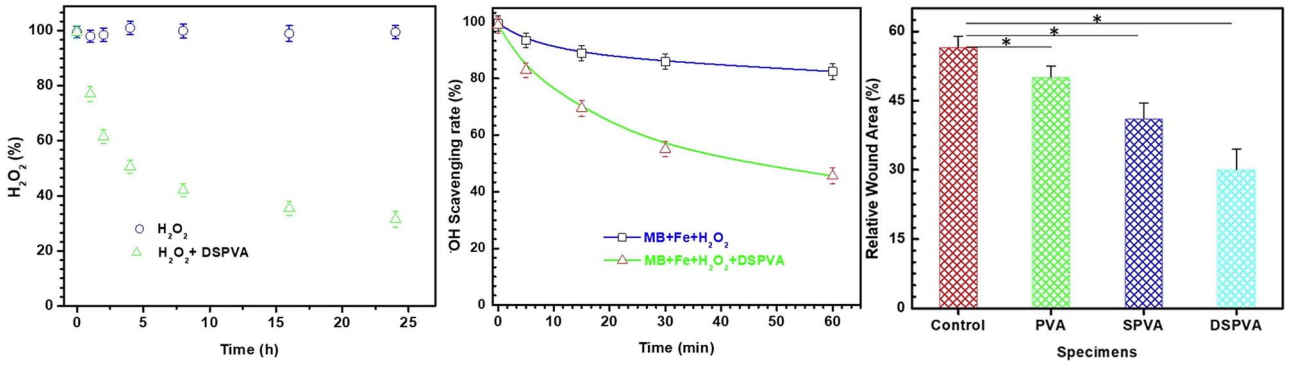


Figure 7 ROS-scavenging performance of gallic acid-functionalized dendrimer-enhanced SF/PVA (DSPVA) hydrogels. Reductions in hydrogen peroxide (H_2O_2; left panel) and hydroxyl radical scavenging capacity measured via methylene blue (MB)/iron (Fe)/H_2O_2 assay (middle panel), and corresponding wound-area reduction (%) in diabetic mice at 10 days post-treatment (right panel). Adapted from Islam *et al*. [54]. *ROS* reactive oxygen species

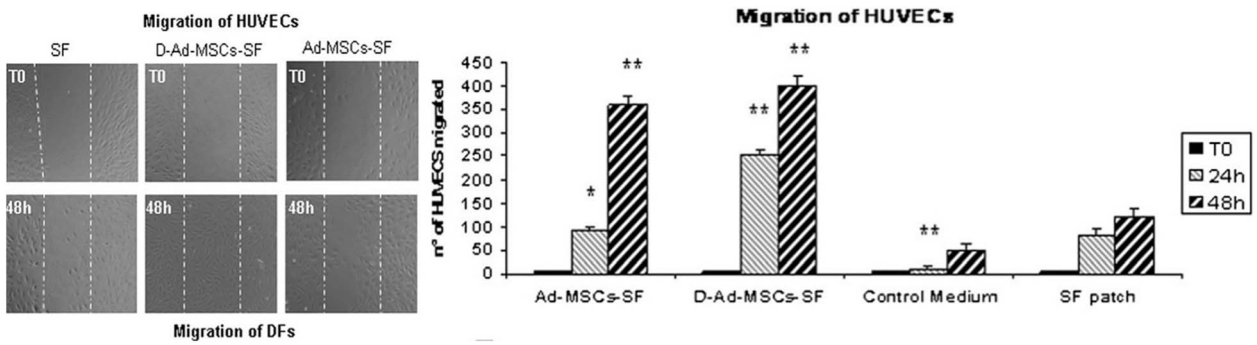


Figure 8 HUVEC migration in scratch assay. Scratch assays showing significantly increased HUVEC migration when co-cultured with cellularized adipose mesenchymal stem cells (AD-MSCs) or decellularized (D-Ad-MSCs) SF scaffolds compared to acellular SF scaffold controls. Adapted from Navone *et al.* [128]. *Ad-MSCs-SF* silk fibroin patch cellularized with human adipose-derived mesenchymal stromal cells, *D-Ad-MSCs-SF* silk fibroin patch after human adipose-derived mesenchymal stromal cells removal (decellularization), *HUVECs* human umbilical vein endothelial cells, *SF* silk fibroin

Decellularized ECM-based scaffolds, by contrast, eliminate the immunogenicity of live cells while retaining matrix-bound bioactive cues and the native ECM architecture for the future desired cell type [125–127]. Navone *et al.* [128] evaluated both cellularized and decellularized ADMSCs SF nanofibrous patches for the treatment of chronic wounds in diabetic mice. Importantly, decellularization, sterilization, freezing, and storing did not affect the SF structure or scaffold integrity. *In vivo* implantation demonstrated rapid wound-area reduction, with both cellularized and decellularized scaffolds achieving ∼40% and 35% closure, respectively, within 3 days and complete wound closure by Days 9–10, compared with 15–17 days for controls. *In vitro* co-culture with human umbilical vein endothelial cells (HUVECs), dermal fibroblasts, and keratinocytes revealed enhanced endothelial migration and release of angiogenic factors, stimulating robust micro-vessel outgrowth (Figure 8).

These findings suggest that SF scaffolds can function as effective delivery platforms for cell-derived regenerative signals even in the absence of viable transplanted cells. Decellularized SF-based constructs may therefore offer a translationally attractive alternative by combining many of the regenerative benefits of cell therapy with improved safety, shelf-life, and regulatory feasibility. Nonetheless, further studies are required to define durability of response, scalability of manufacturing, and comparative efficacy relative to existing acellular advanced wound dressings.

Extracellular matrix proteins and protein additives Incorporating ECM proteins into SF scaffolds can enhance their biological performance. Bogadi *et al.* [129] reviewed the combined use of SF with sericin across various formulations for diabetic wound healing. Although sericin is often removed during degumming due to immunogenicity concerns, studies have shown that sericin's cytotoxicity is highly dependent on purity, molecular weight, and extraction method [130, 131]. When appropriately purified and formulated, sericin has been reported to exhibit anti-inflammatory activity [e.g. suppression of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)], antioxidant properties through free-radical scavenging, antibacterial effects against common wound pathogens (e.g. *Staphylococcus aureus*, *Escherichia coli*), and favorable moisture-retention capacity [132–134]. These findings suggest that sericin, when carefully controlled, may complement SF by contributing biological functionality without compromising scaffold biocompatibility.

In a phase I/II clinical trial, Noda *et al.* [135] evaluated a SF-elastin sponge for the treatment of chronic lower-limb skin ulcers. Despite the small cohort size and patient attrition at early time-points, the dressing remained intact for 14 days without bacterial proliferation. This prolonged residence time suggests a potential reduction in dressing-change frequency compared with conventional options, which often require replacement every 3–7 days. The treatment appeared most effective after the initial post-debridement exudative period, as excessive wound fluid diluted local silk-elastin concentration. Accordingly, the authors recommended delaying application for 2–3 days following surgical debridement. Overall, the SF-elastin sponge demonstrated safety and resistance to bacterial growth, although larger, controlled

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clinical studies are required to define efficacy, optimal timing, and comparative benefit relative to existing advanced dressings.

Mimetic-peptides Mimetic peptides are short, synthetic amino acid sequences designed to replicate the functional domains of larger proteins (e.g. growth factors or ECM proteins) to trigger targeted biological responses while minimizing structural complexity and immunogenic risk. Compared with full-length proteins, mimetic peptides offer improved stability, lower manufacturing cost, and more predictable structure–function relationships.

Yang *et al.* [136] developed and evaluated ultrathin SF nanosheets functionalized with a pro-survival integrin-binding peptide for diabetic wound treatment. The peptide-functionalized SF nanosheets enhanced endothelial and epithelial cell adhesion and survival, reflecting effective presentation of integrin-mediated signaling cues. These nanosheets increased angiogenic gene expression (VEGF, CD31) by$\sim$ 2.5-fold at Day 7. *In vivo*, treated diabetic wounds achieved near-complete closure with visible hair regrowth by Day 21, indicating improved tissue regeneration rather than simple wound contraction. Their transparent, adhesive, and flexible design suggests strong potential as next-generation SF-based dressings for non-healing DFUs.

This study highlights the advantage of combining SF matrices with mimetic peptides, where the scaffold provides structural support and controlled presentation while the peptide delivers targeted biological signaling. However, mimetic peptide strategies remain limited by challenges in optimizing ligand density, orientation, and long-term signal persistence in protease-rich diabetic wound environments. Future studies should directly compare mimetic peptide-functionalized SF scaffolds with full-length growth factor delivery to clarify relative efficacy, durability, and translational value.

Herbal medicines Herbal medicines provide an accessible and biocompatible class of bio-additives for enhancing SF scaffolds. Xu *et al.* [137] fabricated a biodegradable multifunctional nanofiber membrane by electrospinning SF, poly-(L-lactide-co-caprolactone) (PLCL), and Huangbai Liniment (Compound Phellodendron Liquid; CPL). The resulting SF/PLCL/CPL nanofiber membrane exhibited favorable hydrophilicity, degradation behavior, and mechanical properties, promoting fibroblast compatibility while inhibiting bacterial colony formation. *In vivo* studies demonstrated that the functionalized SF/PLCL/CPL membrane improved wound healing in diabetic mice. Mechanistically, the authors reported enhanced activation of the transforming growth factor-β (TGF-β) signaling pathway and increased myofibroblast formation, consistent with accelerated wound contraction and matrix deposition. The scaffold also reduced inflammatory signaling, including downregulation of IL-1β and TNF-α expression, thereby supporting resolution of chronic inflammation.

Additionally, Inpanya *et al.* [138] investigated wound healing in streptozotocin-induced diabetic rats treated with a blended SF/aloe gel film. Their formulation improved delayed healing by enhancing fibroblast attachment and proliferation, while restoring collagen content and organization to levels comparable with normal skin. They concluded that the blended SF/aloe gel film holds strong potential for treating delayed healing associated with diabetic wounds.

Collectively, these studies suggest that incorporation of selected herbal bio-additives into SF matrices can confer antimicrobial, anti-inflammatory, and pro-regenerative effects in diabetic wound models. However, herbal extracts often contain complex and variable chemical compositions, raising challenges related to batch-to-batch reproducibility, dose standardization, and regulatory characterization. Embedding herbal agents within SF scaffolds may partially mitigate these issues by stabilizing active components and enabling controlled local delivery, but further work is required to define pharmacokinetics, safety margins, and translational consistency.

Genetic modification of SF In addition to post-fabrication incorporation of bio-additives, genetic engineering of SF proteins represents an emerging upstream strategy for introducing therapeutic functionality directly during silk biosynthesis. Through transgenic modification of *Bombyx mori*, recombinant bioactive proteins or peptide motifs can be fused to fibroin sequences and expressed in the posterior silk gland under fibroin-specific promoters [139, 140]. This biosynthetic approach enables production of intrinsically functionalized SF fibers in which bioactive motifs are uniformly integrated throughout the material matrix rather than surface-bound or physically entrapped [141].

For chronic DFU applications, this biosynthetic strategy offers several theoretical advantages. Bioactive sequences such as cell-adhesion motifs (e.g. RGD peptides) [142–144], antimicrobial peptides [145, 146], anti-inflammatory cytokine mimetics [147], or growth factor-derived domains [144, 148] may be genetically incorporated into SF to enhance cellular attachment, promote angiogenesis, modulate inflammation, or inhibit bacterial colonization. Unlike post-fabrication surface grafting or blending, genetic incorporation ensures stable presentation of functional motifs without additional chemical crosslinkers or processing steps that may compromise scaffold integrity or bioactivity [141, 144].

From a wound-healing perspective, genetically engineered SF scaffolds could provide sustained biological signaling in the hostile protease-rich and oxidative microenvironment characteristic of chronic DFUs. Embedding therapeutic motifs directly within the SF backbone may enhance resistance to enzymatic degradation while preserving biological function over extended healing timelines.

Nevertheless, challenges remain in optimizing recombinant protein expression without disrupting fibroin assembly or compromising mechanical performance [149]. Large or structurally complex fusion proteins may interfere with β-sheet formation and fiber strength. Additionally, translational considerations—including regulatory oversight of genetically modified organisms, manufacturing scalability, and batch-to-batch reproducibility—must be addressed before clinical implementation [150]. Overall, biosynthetic genetic modification represents a complementary strategy to conventional bio-additive loading approaches. By integrating therapeutic motifs directly into the SF structure, this method expands the design space of multifunctional SF scaffolds while highlighting the need for careful balance between biological functionality, material performance, and translational feasibility.

Collectively, these studies demonstrate that bio-additives can substantially enhance SF scaffold performance in diabetic wound models; however, therapeutic benefits are not uniform across additive classes and translational tradeoffs must be considered. Growth factor-loaded SF dressings consistently accelerate re-epithelialization and granulation tissue formation, but short *in*

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vivo half-life, high cost, and potential risk of off-target angiogenesis raise important questions regarding long-term safety, dosing control, and scalability in DFU care. By contrast, antimicrobial peptides and antibiotics incorporated into SF matrices effectively reduce bacterial burden and biofilm formation, yet repeated or prolonged exposure may promote resistance and/or exert cytotoxic effects on keratinocytes and fibroblasts, particularly at higher local concentrations. Antioxidant-enriched SF hydrogels and composites have shown improved collagen organization and faster closure in diabetic models, but excessive ROS suppression could theoretically interfere with early host-defense signaling and physiological redox-dependent repair pathways.

Taken together, these findings support a decision-oriented approach in which SF bio-additives are selected and dosed based on dominant wound pathophysiology (e.g. perfusion status, microbial burden, and inflammatory state) rather than a one-size-fits-all strategy. For ischemic ulcers characterized by poor perfusion and limited granulation tissue, incorporation of pro-angiogenic cues, such as growth factors (VEGF, bFGF), stem cells, or angiogenic peptides, may help stimulate neovascularization and granulation tissue formation, with careful dose control to avoid aberrant vessel formation. For clinically infected or heavily colonized ulcers, antimicrobial additives (e.g. antibiotics, antimicrobial peptides, and herbal medicines) embedded within SF matrices can reduce bacterial burden and biofilm formation, but should be balanced against resistance risk and local cytotoxicity; combination with systemic antibiotics may be necessary when clinically indicated. For hyper-inflammatory, non-infected ulcers characterized by persistent exudate and stalled healing, SF enriched scaffolds incorporating anti-inflammatory and/or antioxidant agents (e.g. immunomodulatory neuropeptides, ROS-scavenging moieties, or macrophage-polarization modulators) may help dampen excessive M1-biased inflammation and oxidative stress while preserving sufficient host-defense activity.

With respect to synergy, emerging research suggests that carefully designed combinations can act cooperatively rather than merely additively, but robust comparative evidence remains limited. For example, SF nanofibers co-loaded with growth factors and antimicrobials have reported improved closure time and histological architecture; however, many studies rely on small animal cohorts, short follow-up, and limited benchmarking against advanced standard-of-care dressings, limiting conclusions regarding clinical superiority [151, 152]. Accordingly, future work should prioritize head-to-head comparisons against clinically relevant controls, dose–response optimization, and longer-term outcomes (including scar quality and recurrence) to establish durable benefit and translational value.

Beyond silk fibroin-based scaffolds for chronic DFUs treatment

Although SF-based dressings for chronic DFU treatment remain largely in pre-clinical or early translational stages, several non-SF bioactive therapies have advanced further along the clinical pipeline, providing valuable translational context. In 2021 a randomized Phase III clinical trial ($N = 236$) reported that ON101, a topical formulation loaded with two botanical extracts with anti-inflammatory and macrophage-modulating activity, achieved a significantly higher complete healing rate than conventional dressings, specifically for "hard to heal" ulcers (Wagner grade ≥ 2) [153]. In 2024, a clinical study comparing a synthetic electrospun fiber matrix (SEFM) to standard-of-care, reported higher complete-healing rates within a 12-week period in the SEFM-treated groups (74% in the per-protocol population) compared with SOC alone (33%) [154]. Although these therapies are not SF-based, they provide clinically validated evidence that bioactive and/or ECM-mimetic platforms can improve chronic DFU outcomes and illustrate key development milestones for translation. In addition, a recently early-phase clinical trial is evaluating an allogeneic fibroblast-based topical therapy for refractory DFUs, reflecting continued momentum toward cell- and matrix-based approaches in the clinic. Together, these advances highlight a growing clinical shift toward biologically active, mechanism-informed DFU therapies and reinforce the translational potential of SF-based scaffolds as they move toward future clinical evaluation [155]. These examples also illustrate the key translational milestones—scalable good manufacturing practice (GMP), defined mechanisms of action, and randomized comparisons with standard-of-care—that SF-based platforms must achieve to reach comparable clinical validation, as discussed further in the "Current limitations and future directions" section.

Wound healing mechanisms of SF

SF can contribute to multiple phases of the wound-healing process, from hemostasis through remodeling, by providing both a provisional matrix and biologically interactive cues. During the initial hemostatic stage, SF promotes rapid platelet adhesion and aggregation, facilitating clot formation through activation of the coagulation cascade [79]. This early clot not only halts bleeding but also forms a provisional matrix that stabilizes the wound and supports early cellular infiltration.

As the process transitions into the inflammatory and proliferative phases, SF provides a biomimetic ECM-like environment that delivers biochemical cues and physical scaffolding to support cell adhesion, migration, and proliferation [156, 157]. Integrin-mediated interactions guide keratinocyte and fibroblast migration into the wound bed, initiating re-epithelialization and granulation tissue formation. Simultaneously, SF supports endothelial cell migration and angiogenesis, in part by indirectly enabling the localized and sustained release of angiogenic factors such as VEGF [48]. The material also modulates cytokine and other growth factor signaling, enhancing cellular proliferation and coordinated tissue regeneration [79].

At the molecular level, SF modulates several key signaling pathways central to inflammation and repair. One major target is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which activates and regulates inflammation, cell survival, and tissue remodeling [158]. SF interacts with upstream mediators such as TNF and Toll-like receptors to activate NF-κB, thereby increasing the expression of cytokines (e.g. IL-1β, IL-10), growth factors (e.g. VEGF, EGF), and structural proteins such as fibronectin [26]. This modulation promotes a balanced inflammatory response that is sufficient to clear debris and pathogens while preventing excessive inflammation and tissue degradation. Beyond NF-κB, SF may then engage through additional signaling cascades involved in wound repair, including Wnt, Notch, mitogen-activated protein kinase (MAPK), and the AKT/mTOR pathway [26]. These signaling networks coordinate processes such as cell growth, migration, survival, and remodeling [159]. For example, MAPK and AKT/mTOR signaling enhance fibroblast activity and angiogenesis, while TGF-β, regulated

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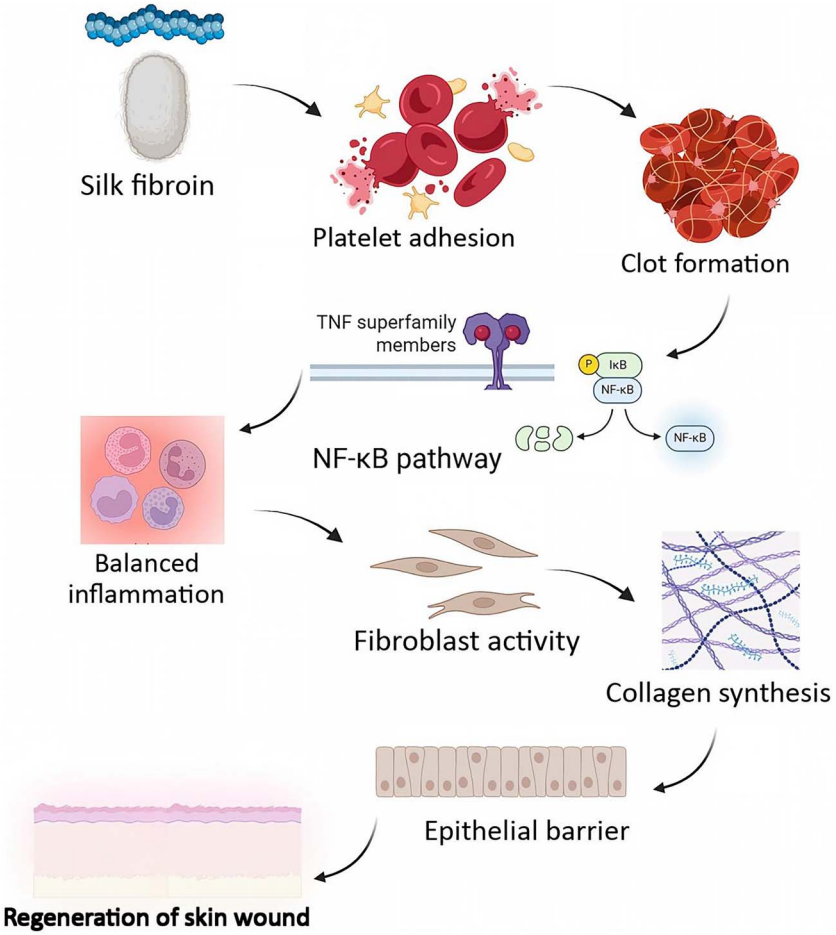


Figure 9 Schematic representation of the wound-healing mechanisms of SF across the hemostatic, inflammatory, proliferative, and remodeling phases. SF promotes platelet aggregation, supports cell migration and angiogenesis, and modulates key signaling pathways (e.g. NF-κB, MAPK, AKT/mTOR) to balance inflammation and enhance tissue regeneration [created with BioRender.com]. Adapted from Aldahish *et al.* [26].

in part by NF-κB, promotes collagen synthesis and matrix deposition during the remodeling phase [160]. By modulating these interconnected signaling networks, SF fosters a healing environment that efficiently transitions from inflammation to tissue remodeling, thereby preventing the chronic, non-healing cascade characteristic of diabetic wounds (Figure 9).

Collectively, these mechanisms support SF as more than a passive structural scaffold (e.g. bandage or gauze); rather, SF can function as an active biological modulator of wound healing that helps shape inflammation, angiogenesis, and ECM remodeling in complex, non-healing wounds such as chronic DFUs.

Current limitations and future directions

After a thorough analysis of bio-enhanced SF for chronic DFU treatment, one challenge remains clear: clinical translation. Despite extensive preclinical validation, the vast majority of SF-based bioactive wound dressings remain at the laboratory or early translational stage. Among the studies reviewed, only two reached the clinical trial stage, and even those trials focused primarily on safety with only preliminary insights into efficacy.

A major barrier to translation is the lack of accurate, sophisticated, and predictive preclinical models. Commonly used rodent models, particularly mouse and rat, fail to recapitulate the size, chronicity, biomechanics, vascular insufficiency, and neuropathy characteristic of human DFUs. As a result, promising preclinical outcomes may overestimate therapeutic performance in patients. Regulatory complexity further slows progress. Chemical or biological modification of SF to enhance therapeutic performance can alter its classification and trigger additional regulatory scrutiny. Multicomponent bio-enhanced dressings, particularly those combining biomaterials, biologics, and/or cells, face challenges in regulatory designation as devices, drugs, or combination products, complicating approval pathways.

Scale-up manufacturing of natural polymers such as silk from bench to bedside presents further hurdles. First, batch-to-batch variability arises from differences in cocoon source, degumming conditions, dissolution protocols, and processing parameters, all of which influence β-sheet content, mechanical properties, degradation rate, and release kinetics [161]. Sterilization methods such as gamma irradiation, ethylene oxide exposure, or autoclaving may further alter SF secondary structure or scaffold architecture. These factors complicate shelf-life determination, storage stability, and reproducibility under GMP conditions [162]. Lastly, an intrinsic limitation of natural polymers is the difficulty in precisely controlling molecular weight and structural uniformity, which can influence degradation profiles, mechanical properties, and release kinetics, thereby complicating shelf-life and storage stability [59].

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Bio-enhanced SF scaffolds also face challenges related to the short half-life of many growth factors, mimetic peptides, and antioxidants, which degrade rapidly *in vivo.* Achieving controlled and sustained release remains difficult, particularly within the enzymatically active, oxidative, and microbially-rich environment of DFUs. More studies are needed to validate sustained (weeks-long) release profiles without premature degradation to better reflect clinical healing timelines [163]. To address these challenges, research efforts are increasingly focused on nanoparticles, microspheres, and other secondary carrier systems to support sustained, controlled delivery. However, the long-term safety, biodistribution, clearance, and off-target effects of these delivery vehicles remain insufficiently characterized [164, 165].

Interest has also grown in "smart" or stimulus-responsive SF dressings capable of releasing therapeutic agents in response to internal wound cues or external stimuli such as pH, temperature, ROS, or enzymatic activity [53]. While these approaches hold tremendous promise for improving therapeutic precision and reducing off-target effects, they remain largely experimental. Translation is constrained by material stability in wound exudate, system complexity, cost, and regulatory burden associated with integrating sensing, delivery, or responsive components into a biocompatible, clinically-viable format [166].

Several non-SF-based therapies have advanced further than the presented Phase I/II trials of Nanordica [115] and Noda *et al.*'s silk-elastin sponge [135]. Examples include ON101 [167] and commercially available bioactive dressings such as Apis® from SweetBio [168], which have followed clear development pathways involving scalable GMP manufacturing, defined mechanisms of action, early human safety studies, and randomized comparisons with standard-of-care. These examples highlight the translational milestones that SF-based platforms must achieve to reach comparable clinical validation.

Although bio-enhanced SF scaffolds have demonstrated consistent and robust acceleration of wound closure in diabetic animal models, they should currently be viewed as promising next-generation candidates rather than clinically validated alternatives. Critical gaps remain, including head-to-head comparisons with approved advanced dressings, pharmacoeconomic analyses, standardized usability assessments, and long-term recurrence data.

Future research should prioritize the development of physiologically relevant DFU models that better capture chronicity, perfusion deficits, infection burden, neuropathy, and mechanical loading. Advanced platforms such as bioengineered skin equivalents, organ-on-a-chip systems, humanized mouse models, and large-animal wound models may improve predictive accuracy and translational relevance by more closely recapitulating the chronicity, perfusion deficits, and biomechanical environment of human DFUs. Several groups have attempted to enhance rodent DFU models by incorporating ischemia, neuropathy, or infection [169, 170]. While these approaches partially recapitulate delayed healing and impaired angiogenesis, rodents still heal predominantly by wound contraction rather than re-epithelialization, limiting clinical extrapolation.

Future studies should also incorporate larger wound sizes and extended follow-up periods to evaluate long-term outcomes including scar quality, recurrence rates, tissue integration, and functional restoration. This data will help bridge the gap between bench and bedside, and will be essential for regulatory approval and clinical adoption.

Beyond the static bio-additive incorporation discussed within this review, future SF-based DFU dressings may incorporate microenvironment-responsive ("smart") functionalities capable of modulating therapeutic delivery in response to wound-specific cues such as alkaline pH, elevated ROS, or excessive protease activity [89, 171, 172]. Stimuli-responsive SF hydrogels have demonstrated proof-of-concept efficacy in diabetic wound models, where pH [173] or ROS-triggered [174] systems enhanced antibacterial activity or antioxidant effects, respectively. However, DFU exudate is highly protein-rich and protease-abundant, which may induce premature degradation, signal instability, or uncontrolled therapeutic release in responsive systems [172, 175, 176]. Accordingly, successful future smart SF dressings must demonstrate robustness, manufacturability, and clear therapeutic advantages over simpler sustained-release platforms to justify their added complexity.

Finally, successful translation of SF-based DFU therapies will require close collaboration across materials science, bioengineering, molecular biology, and clinical medicine. Integrating mechanistic insight with scalable manufacturing and clinically meaningful endpoints will be critical to advancing SF scaffolds from experimental constructs to practical wound-care solutions. As understanding of DFU pathophysiology deepens, SF-based platforms, if rigorously validated, may ultimately contribute to more personalized, stage-specific treatment strategies for chronic diabetic wounds.

Conclusions

Bio-enhanced SF scaffolds have demonstrated consistent, reproducible acceleration of wound closure across a range of preclinical models, positioning them as compelling candidates for next-generation DFU care. The chemical and structural versatility of SF—enabling tunable degradation, sustained bioactive delivery, and compatibility with diverse additive classes including growth factors, antimicrobials, antioxidants, and cell-derived signals—makes it uniquely suited to address the multifactorial pathophysiology of chronic DFUs. However, the field stands at a translational inflection point. The gap between preclinical promise and clinical validation remains substantial, constrained by the limited predictive accuracy of current wound models, regulatory complexity surrounding multicomponent biologic-device constructs, and the practical challenges of GMP-scale manufacturing. Closing this gap will require not only improved preclinical platforms that better recapitulate human DFU chronicity, perfusion deficits, and neuropathy, but also rigorous head-to-head comparisons with approved advanced dressings and long-term outcome data including recurrence and functional restoration. As the field matures, the most impactful SF-based strategies will likely be those designed around wound stage and dominant pathophysiology; matching the scaffold's therapeutic profile to the patient's wound rather than applying a uniform approach. Achieving this vision will demand sustained collaboration across biomaterials science, wound biology, and clinical medicine. Ultimately, the measure of success for these platforms will not be technical sophistication but whether they reduce amputation rates, restore

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function, and improve quality of life for the millions of patients living with chronic diabetic wounds.

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Conflicts of interest

Not applicable.

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