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Integrating Microbial Exopolysaccharides (EPS) with Growth Factors for Enhanced Antimicrobial and Angiogenic Wound Healing

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ABSTRACT

Chronic wounds, including diabetic foot ulcers, venous leg ulcers, and pressure ulcers, represent a major clinical challenge due to persistent microbial infection, prolonged inflammation, impaired angiogenesis, and delayed tissue regeneration. Conventional wound care strategies often fail to address these interconnected pathological factors simultaneously, resulting in poor healing outcomes and high recurrence rates. Microbial exopolysaccharides (EPS) have emerged as promising biomaterials for wound healing due to their biocompatibility, moisture-retention capacity, antimicrobial barrier properties, and extracellular matrix-mimicking structure. In parallel, growth factors such as vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, and epidermal growth factor play essential roles in regulating angiogenesis, cell proliferation, and tissue remodeling. However, direct application of growth factors is limited by rapid degradation, poor localization, and uncontrolled release in protease-rich chronic wound environments. Integrating growth factors within EPS-based matrices offers a multifunctional therapeutic strategy that combines antimicrobial protection, structural support, and sustained pro-regenerative signaling. The EPS-GF composite systems enable localized and controlled growth factor delivery, promote neovascularization, enhance extracellular matrix deposition, and reduce microbial burden at the wound site. Preclinical studies consistently demonstrate accelerated wound closure and improved tissue quality using these integrated platforms compared to conventional dressings or single-component therapies. This review primarily focuses on bacteria-derived EPS, with limited discussion of selected fungal EPS relevant to wound healing applications., Also discusses their biological roles, strategies for their integration, mechanistic insights into their synergistic action, and recent preclinical advances. Despite their strong therapeutic potential, challenges related to large-scale production, growth factor stability, regulatory approval, clinical translation remain and must be addressed to enable widespread clinical adoption. Overall, EPS-GF composites represent a next-generation approach for advanced wound management with strong potential for clinical translation.

KEYWORDS

Chronic wound healing, microbial exopolysaccharides, growth factor delivery, antimicrobial hydrogels, angiogenesis, tissue regeneration

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INTRODUCTION

Chronic wounds, including diabetic foot ulcers, pressure injuries, and severe burn lesions, remain a major clinical problem due to delayed healing, high infection risk, and substantial healthcare costs[1-7]. Unlike acute wounds that progress through orderly healing phases, chronic wounds frequently remain in a prolonged inflammatory state marked by excessive protease activity, elevated reactive oxygen species, and impaired angiogenesis[1,2]. Chronic wounds are characterized by persistent microbial colonization, excessive inflammatory responses, and disrupted angiogenic signaling, which collectively delay tissue regeneration and wound closure[8]. Microbial colonization and host microbiota dysregulation can significantly influence inflammation and tissue repair outcomes in chronic wound environments[9]. Persistent microbial colonization, particularly by biofilm-forming pathogens, further sustains inflammation and restricts cellular migration, creating a vicious cycle that conventional therapies rarely resolve[3]. Standard wound dressings provide moisture and protection but do not address these underlying biological dysfunctions[4].

Microbial exopolysaccharides (EPS) have emerged as promising biomaterials for chronic wound management due to their biocompatibility, natural origin, and multifunctionality[5,6]. The EPS forms hydrated hydrogel networks that mimic the extracellular matrix (ECM), supporting cell adhesion, migration, and proliferation while maintaining a moist wound environment. Several EPS, including bacterial cellulose, xanthan, hyaluronic acid, and dextran derivatives, also exhibit intrinsic antimicrobial activity through inhibition of bacterial adhesion, biofilm disruption, or immune modulation[5,6], making them effective structural and protective scaffolds.

Growth factors (GF), such as VEGF, PDGF, FGF, and EGF, are central regulators of angiogenesis, fibroblast activity, extracellular matrix deposition, and epithelialization[7]. However, their clinical use is limited by rapid degradation, short half-life, and uncontrolled release. Incorporation of growth factors into EPS-based hydrogels enables sustained and localized delivery while protecting bioactivity and maintaining an ECM-like microenvironment conducive to neovascularization and tissue repair[6,7].

Chronic wounds persist through interconnected processes of infection, inflammation, and poor vascularization. As illustrated in Fig. 1, chronic wounds are characterized by a self-perpetuating vicious cycle involving persistent bacterial biofilm formation, prolonged inflammation, impaired angiogenesis, and delayed tissue remodeling. The schematic highlights how EPS-GF composite hydrogels intervene in this cycle by providing an antimicrobial barrier, enabling sustained growth factor release, promoting neovascularization, and supporting cellular proliferation and tissue regeneration. The EPS-GF composites are designed to disrupt this cycle by integrating antimicrobial protection, controlled pro-regenerative signaling, and structural support. This review examines the biological basis of wound healing, the functional roles of microbial EPS and growth factors, recent advances in EPS-GF composite systems, and strategies for their integration into multifunctional wound therapies to support clinical translation.

To ensure a structured and comprehensive narrative review, a literature search was conducted focusing on microbial exopolysaccharide (EPS)-based growth factor delivery systems for wound healing applications. Relevant studies were identified using electronic databases, including PubMed, Scopus, and Web of Science. Additional articles were retrieved through manual screening of reference lists from selected publications to ensure broader coverage of relevant literature.

Search terms were formulated using combinations of keywords and Boolean operators, including “microbial exopolysaccharides”, “bacterial cellulose”, “dextran”, “xanthan”, “hyaluronic acid”, “growth factor delivery”, “VEGF”, “PDGF”, “FGF”, “EGF”, “chronic wounds”, and “angiogenesis”. These terms were used to capture studies addressing both the antimicrobial and regenerative roles of EPS-based systems.

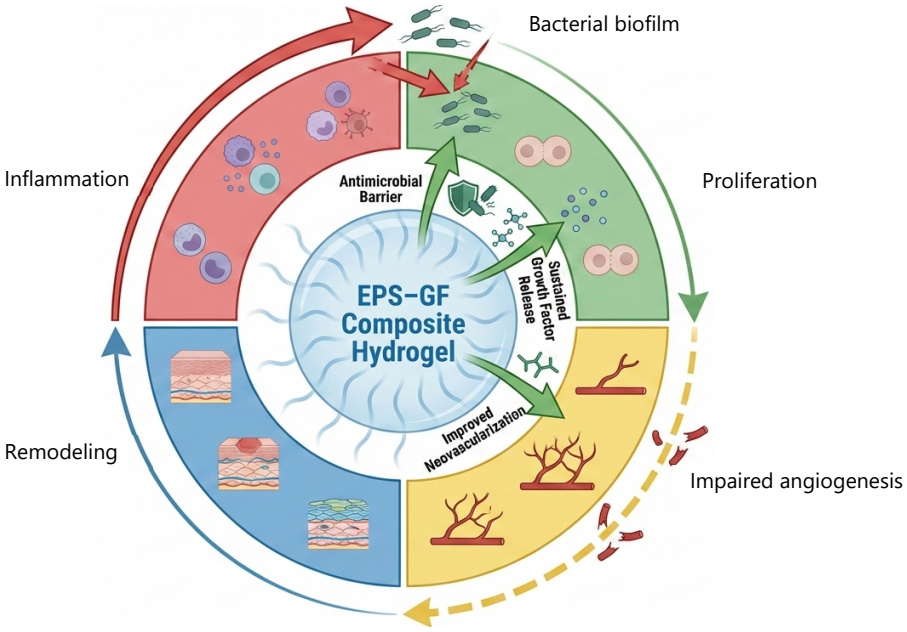

Fig. 1: Schematic illustration of the chronic wound vicious cycle and EPS-GF intervention methodology

Peer-reviewed articles published in English between 2000 and 2025 were included. Studies were selected based on their relevance to microbial-derived EPS materials in wound healing, particularly those involving growth factor incorporation and reporting biological or therapeutic outcomes. Duplicate records, conference abstracts, non-peer-reviewed sources, and studies unrelated to wound healing were excluded.

Both *in vitro* and *in vivo* preclinical studies were considered, along with relevant clinical reports where applicable. Study selection was performed through title and abstract screening, followed by full-text evaluation based on relevance to the review scope. Extracted information was organized according to EPS type, growth factor involved, delivery strategy, biological performance, and translational relevance. The findings were synthesized qualitatively to highlight key mechanistic insights and recent advancements in the field[10].

MICROBIAL EXOPOLYSACCHARIDES (EPS) IN WOUND HEALING

Microbial exopolysaccharides (EPS) are high-molecular-weight polysaccharides produced by bacteria and fungi that have gained increasing attention in wound healing due to their multifunctional properties[11,12]. The EPS readily forms hydrated hydrogel networks that mimic the extracellular matrix (ECM), providing structural support, maintaining a moist wound environment, and facilitating cellular infiltration necessary for tissue repair[13]. Microbial exopolysaccharides provide a hydrated three-dimensional matrix that mimics native extracellular matrix architecture while simultaneously acting as a protective antimicrobial barrier[8]. Their physicochemical properties, including viscosity, mechanical strength, and degradation rate, can be tuned by modifying monosaccharide composition and molecular architecture[14].

There are many kinds of EPS investigated for wound healing, including hyaluronic acid (HA), dextran, xanthan, bacterial cellulose (BC), alginate, and gellan gum. HA regulates inflammation, promotes angiogenesis, and supports fibroblast proliferation while maintaining hydration[15]. Dextran-based hydrogels exhibit good biocompatibility with mild antimicrobial effects that reduce infection risk[16]. Xanthan functions as a scaffold and viscosity modifier with inhibitory effects on bacterial growth[17]. The BC is distinguished by its high tensile strength, nanofibrillar structure, and excellent water retention, making it an effective regenerative scaffold[16]. Alginate and gellan gum form ionically crosslinked hydrogels that maintain moisture and support cell adhesion and controlled delivery of bioactive agents[17].

Table 1: Selected microbial eps and their dual functions in wound healing

EPS type	Source	Primary antimicrobial mechanism	Pro-regenerative function	Suitability for GF incorporation	Key references
Hyaluronic acid	*Streptococcus* spp.	Inhibits bacterial adhesion; hydration barrier	Promotes angiogenesis and cell migration	Excellent	Wan *et al.*[13] and Litwiniuk *et al.*[15]
Bacterial cellulose	*Komagataeibacter* spp.	Physical microbial barrier	Supports angiogenesis and granulation	Excellent	Arslan *et al.*[6] and Boateng *et al.*[19]
Dextran	*Leuconostoc* spp.	Reduces biofilm formation	Enhances fibroblast activity	Good	Portela *et al.*[16]
Xanthan gum	*Xanthomonas campestris*	Limits microbial colonization	Maintains moist wound environment	Moderate	Bharathi and Lee[11] and Lee and Mooney[17]
Alginate (microbial)	*Azotobacter* spp.	Gel barrier against microbes	Supports cell proliferation	Good	Boateng *et al.*[19] and Tan *et al.*[20]
Pullulan	*Aureobasidium pullulans*	Prevents bacterial attachment	Enhances epithelialization	Moderate	Boateng *et al.*[19]

The EPS show antimicrobial activity by limiting microbial adhesion, disrupting biofilm formation, and modulating host immune responses[11,13]. Additionally, microbial-derived biotherapeutics such as next-generation probiotics may indirectly support wound healing by modulating host immunity and inflammation[18]. The BC hydrogels, for example, restrict colonization by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, while xanthan and dextran derivatives indirectly suppress bacterial growth by enhancing host defenses[16,17,19].

Beyond infection control, EPS actively supports angiogenesis and tissue regeneration. HA enhances endothelial cell migration and neovascularization[15], while BC and gellan gum provide scaffolding for fibroblast attachment, collagen deposition, and granulation tissue formation[19,20].

The EPS hydrogels are also well suited for growth factor loading. Hydrophilic networks can entrap VEGF, PDGF, FGF, and EGF, enabling controlled and sustained release[13]. Release behavior can be regulated through crosslinking density and degradation rate[14], while covalent conjugation in BC or modified HA further stabilizes growth factors and prolongs bioactivity[15].

As summarized in Table 1, microbial EPS combine antimicrobial activity, pro-regenerative function, and compatibility with growth factor incorporation. Chemical or enzymatic modifications such as sulfation, acetylation, or crosslinking further enhance mechanical properties and bioactivity[16]. The EPS can also act as carriers for additional bioactive agents, including antimicrobial peptides or nanoparticles, enabling multifunctional wound dressings[16].

From my perspective, microbial EPS represent a versatile and adaptable platform for chronic wound healing, offering structural support, antimicrobial protection, and effective growth factor delivery beyond what conventional dressings can provide.

GROWTH FACTORS IN WOUND HEALING

Growth factors (GFs) are important signaling molecules that control significant steps in tissue repair, such as cell proliferation, migration, angiogenesis, and extracellular matrix deposition[21,22]. They are main controllers of both acute and chronic wound healing, coordinating cellular responses and tissue regeneration. Some of the most important growth factors involved in wound repair include Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and Epidermal Growth Factor (EGF), which act through complementary mechanisms[23]. However the protease-rich microenvironment of chronic wounds significantly reduces growth factor bioavailability, limiting their therapeutic efficacy when administered directly[8].

The VEGF drives angiogenesis by stimulating endothelial cell proliferation and capillary formation, restoring vascular supply in ischemic wounds[24]. It is a critical biological process for tissue regeneration in chronic wound environments[25]. The PDGF promotes fibroblast recruitment, proliferation, and matrix production, supporting granulation tissue formation[26]. The FGF exhibits broad mitogenic effects on fibroblasts, keratinocytes, and endothelial cells, facilitating both neovascularization and epithelialization[27], while EGF accelerates wound closure by enhancing keratinocyte migration and proliferation.

Despite their therapeutic potential, free growth factors show limited clinical efficacy due to rapid enzymatic degradation, short half-life, and instability within the chronic wound microenvironment[24,26]. Uncontrolled or burst release can also cause off-target effects such as fibrosis or abnormal angiogenesis, often requiring repeated or high-dose administration[27].

To overcome these limitations, controlled delivery strategies have been developed, including physical entrapment in hydrogels, covalent conjugation to polymeric scaffolds, and affinity-based binding via heparin or related interactions[21,22]. These approaches improve growth factor stability and enable sustained, localized release while preserving bioactivity[23].

Chronic wounds are also marked by higher protease activity and persistent inflammation, which reduce growth factor bioavailability[24]. Oxidative stress and excessive reactive oxygen species further disrupt angiogenic signaling and delay healing processes[28]. Incorporation into EPS-based hydrogels provides a protective, ECM-like reservoir that preserves growth factor activity and allows modulation of release kinetics through network density, porosity, and degradation rate[26]. Sequential or staged release can better mimic physiological healing, with early PDGF-driven fibroblast recruitment followed by VEGF-mediated angiogenesis and EGF-induced epithelialization[27].

Consistent preclinical evidence shows that growth factor-loaded hydrogels outperform free growth factor delivery, significantly enhancing angiogenesis, granulation tissue formation, fibroblast proliferation, and collagen deposition in diabetic wound models[21,27].

In conclusion, while growth factors are essential for wound healing, their clinical application is limited by instability and rapid degradation. The EPS-based hydrogels enable controlled, localized delivery and sustained bioactivity, forming the foundation for effective EPS-GF composite systems in chronic wound therapy.

EPS-GF COMPOSITE STRATEGIES

The integration of growth factors (GFs) into microbial exopolysaccharide (EPS) matrices represents a sophisticated approach to addressing the dual challenges of infection control and tissue regeneration in chronic wounds[29]. Incorporating growth factors within biopolymeric matrices enhances their localized retention, promotes sustained release kinetics, and improves angiogenic and regenerative outcomes[8]. The EPS-GF composites leverage the structural and antimicrobial properties of EPS while providing controlled, localized delivery of bioactive growth factors[30]. Several strategies have been developed to incorporate growth factors into EPS hydrogels, primarily categorized into physical entrapment, covalent conjugation, and affinity-based binding. Each method offers distinct advantages and limitations.

Physical entrapment: Physical entrapment involves incorporating growth factors directly within the hydrogel matrix during scaffold formation. The EPS network retains the growth factors and allows gradual diffusion over time, maintaining bioactivity without chemical modification[31]. This method is straightforward and preserves protein structure but may lead to an initial burst release, potentially limiting sustained therapeutic efficacy. The EPS types such as bacterial cellulose, hyaluronic acid, and alginate are well-suited for physical entrapment due to their high water content, mechanical stability, and biocompatibility.

Table 2: Comparison of growth factor integration strategies in EPS matrices

Method	GF examples	Release kinetics	Advantages	Limitations	Key references
Physical entrapment	VEGF, FGF	Burst+diffusion-controlled	Simple, preserves bioactivity	Poor long-term control	Li *et al.*[22] and Peppas *et al.*[31]
Covalent conjugation	VEGF, PDGF	Sustained, minimal burst	High stability, localized delivery	Possible loss of bioactivity	Richardson *et al.*[32]
Affinity-based binding	VEGF, FGF	Reversible, controlled	Mimics ECM regulation	Complex fabrication	Ruel-Gariépy and Leroux[33]
Microparticle-in-hydrogel	VEGF, EGF	Multi-phase release	Excellent GF protection	Fabrication complexity	Zhang *et al.*[29] and Tonnesen *et al.*[34]

VEGF: Vascular Endothelial Growth Factor (primarily responsible for stimulating the growth of new blood vessels), FGF: Fibroblast Growth Factor (involved in angiogenesis, wound healing, and embryonic development). PDGF: Platelet-Derived Growth Factor (plays a significant role in blood vessel formation and cell growth) and EGF: Epidermal Growth Factor (plays an important role in the regulation of cell growth, proliferation, and differentiation)

Covalent conjugation: Covalent conjugation chemically links growth factors to functional groups on EPS polymer chains. This strategy enhances growth factor stability, reduces enzymatic degradation, and provides a predictable, sustained release profile[32]. Functional groups such as amines or carboxyls on EPS can be modified to bind VEGF or PDGF, stabilizing the protein within the hydrogel. While covalent conjugation offers superior control over release kinetics, it requires careful optimization to avoid altering growth factor bioactivity. Chemically modified EPS, including thiolated hyaluronic acid or carboxymethyl dextran, have been successfully employed for covalent immobilization of growth factors[32].

Affinity-based binding: Affinity-based binding utilizes specific interactions between growth factors and binding motifs incorporated into the EPS matrix. Heparin-like domains or engineered binding sites can reversibly capture growth factors such as VEGF and FGF, allowing controlled release in response to environmental signals[33]. This approach mimics natural extracellular matrix regulation, enabling temporal and spatial presentation of growth factors without covalent modification. It is particularly useful for sequential or gradient-based delivery, aligning with the wound healing process.

Comparison of strategies: Table 2 summarizes these EPS-GF integration strategies, including method, representative growth factors, release kinetics, advantages, and limitations. Physical entrapment is simple and preserves bioactivity but can result in burst release. Covalent conjugation ensures long-term stability but requires chemical modification. Affinity-based binding allows reversible, temporally controlled release but is more complex to engineer. Selection of the appropriate strategy depends on the wound type, desired release profile, and specific EPS properties.

Design considerations: Hydrogel performance depends on EPS type, crosslinking density, porosity, degradation rate, and mechanical properties[29]. Hydrogels must balance structural integrity with flexibility to conform to irregular wound surfaces while maintaining hydration. Combining multiple EPS types or blending with secondary polymers can optimize scaffold properties, enhancing growth factor retention, antimicrobial activity, and tissue regeneration potential[30]. Figure 2 illustrates representative EPS-GF hydrogel designs: (1) Physically entrapped growth factors, (2) Covalently linked growth factors, and (3) growth factors incorporated via microparticles or affinity domains within the EPS matrix. The figure highlights how integration strategies influence spatial distribution, release kinetics, and cellular interactions at the wound site. Preclinical studies have demonstrated the efficacy of EPS-GF composites in accelerating wound closure and promoting angiogenesis. The VEGF-loaded bacterial cellulose hydrogels enhance neovascularization and granulation tissue formation, while PDGF-incorporated hyaluronic acid scaffolds promote fibroblast proliferation and epithelialization more effectively than free growth factor application[29,30]. Furthermore, EPS-GF composites can be engineered for stimuli-responsive release. pH-sensitive or enzyme-responsive hydrogels can selectively release growth factors in response to

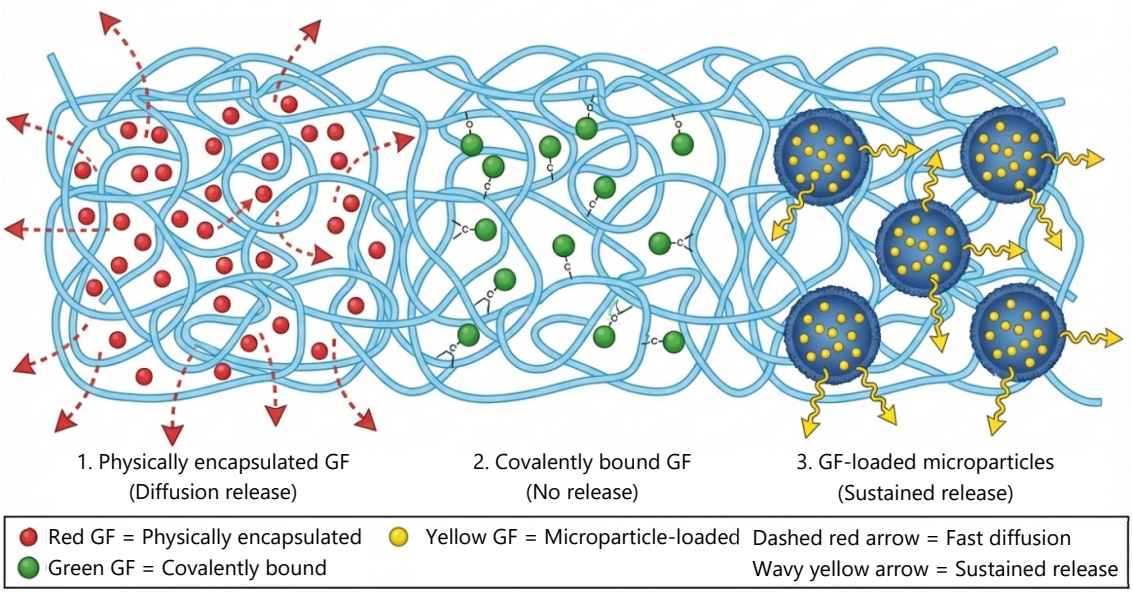

Fig. 2: EPS hydrogel illustrating physical entrapment, covalent conjugation, and affinity-based growth factor delivery

wound-specific cues, enhancing therapeutic precision[33]. Overall, EPS-GF composites offer a multifunctional platform capable of simultaneously providing antimicrobial protection, sustained growth factor delivery, and structural support for tissue regeneration. Careful selection of EPS type and incorporation strategy allows the design of scaffolds tailored to specific wound types, maximizing therapeutic efficacy while minimizing systemic exposure and complications.

MECHANISTIC INSIGHTS AT THE WOUND BED

The EPS-GF composites work by combining antimicrobial protection, structural support, and controlled growth factor delivery at the wound site[34]. Chronic wounds often suffer from bacterial colonization, biofilm formation, and poor angiogenesis, which hinder healing. The EPS hydrogels act as a physical barrier, preventing bacterial adhesion and biofilm formation, while maintaining a hydrated environment that supports cell migration[35]. Their nanofibrillar or crosslinked structure also improves scaffold porosity and mechanical strength, aiding fibroblast and endothelial cell infiltration and extracellular matrix deposition.

Sustained release of growth factors ensures continuous signaling to cells. The VEGF promotes endothelial proliferation, migration, and tube formation, supporting neovascularization[34]. The PDGF and FGF recruit fibroblasts, enhance collagen synthesis, and stimulate epithelial proliferation. By controlling release kinetics, EPS-GF composites maintain effective concentrations over time, addressing the low natural growth factor levels in chronic wounds.

The EPS matrices can be engineered to respond to environmental cues. The pH-sensitive hydrogels release growth factors in acidic wound conditions, while enzyme-responsive scaffolds degrade in the presence of wound-specific proteases, triggering local GF release[35]. This targeted delivery enhances precision and efficacy.

At the cellular level, EPS-GF scaffolds reduce bacterial load and inflammation, allowing keratinocytes, fibroblasts, and endothelial cells to proliferate efficiently. Embedded growth factors stimulate angiogenesis and extracellular matrix deposition, accelerating granulation tissue formation. This synergistic effect interrupts the chronic wound cycle, promoting re-epithelialization, neovascularization, and functional tissue repair[34].

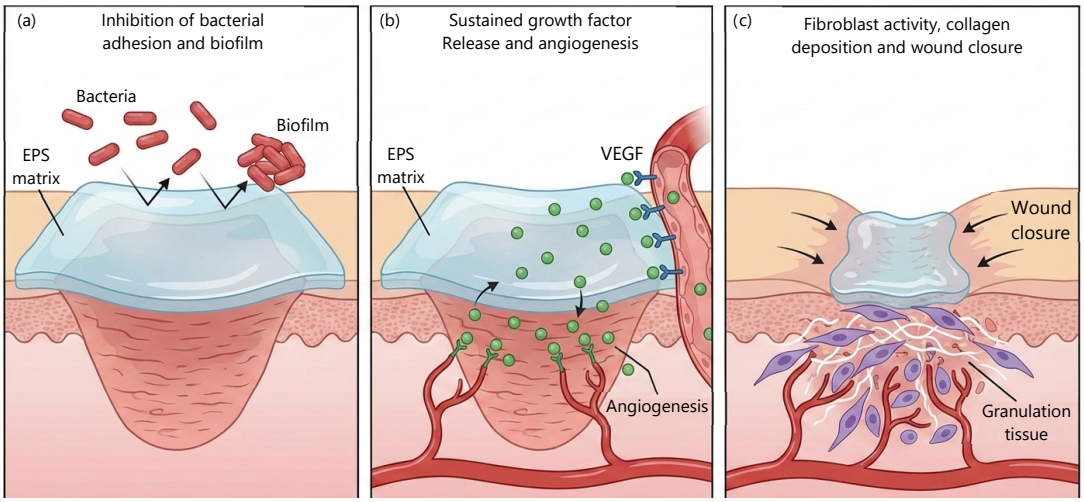

Fig. 3(a-c): Mechanistic diagram showing EPS-GF composite action at the wound interface (a) Inhibition of bacterial adhesion and biofilm (b) Sustained growth factor release and angiogenesis and (c) Fibroblast activity, collagen deposition and wound closure

Table 3: Summary of recent preclinical studies using EPS-GF composites

EPS type	Growth factor	Wound model	Key outcome	Key references
Bacterial cellulose	VEGF	Diabetic rat wound	Enhanced angiogenesis and faster closure	Schultz and Wysocki[37]
Hyaluronic acid	PDGF	Full-thickness rat wound	Increased fibroblast proliferation	Schultz and Wysocki[37]
Xanthan gum	FGF	Ischemic wound	Improved granulation tissue	Zhang *et al.*[29]
Dextran	VEGF	Infected wound	Reduced bacterial load, better vascularization	Jayakumar *et al.*[38]
Chitosan-EPS blend	EGF	Diabetic mouse wound	Accelerated re-epithelialization	Boateng *et al.*[19]
Alginate-EPS composite	VEGF	Chronic wound	Sustained GF release, higher capillary density	Ruel-Gariépy and Leroux[33]

VEGF: Vascular Endothelial Growth Factor (primarily responsible for stimulating the growth of new blood vessels), FGF: Fibroblast Growth Factor (involved in angiogenesis, wound healing, and embryonic development), PDGF: Platelet-Derived Growth Factor (plays a significant role in blood vessel formation and cell growth) and EGF: Epidermal Growth Factor (plays an important role in the regulation of cell growth, proliferation, and differentiation)

Figure 3 illustrates this mechanism: (A) EPS inhibits bacterial adhesion and biofilms, (B) growth factors like VEGF stimulate angiogenesis, and (C) fibroblast activity drives collagen deposition and wound closure.

In summary, EPS-GF composites provide antimicrobial protection, sustained growth factor signaling, and structural support, overcoming the main limitations of conventional dressings and free growth factor therapies[34-36].

PRECLINICAL AND EXPERIMENTAL EVIDENCE OF EPS-GF COMPOSITES

Recent preclinical studies demonstrate the efficacy of EPS-GF composites in chronic wound models, particularly diabetic, ischemic, and infected wounds[37]. In diabetic rodent models, VEGF-loaded bacterial cellulose hydrogels significantly enhanced angiogenesis, granulation tissue formation, and wound closure compared to free VEGF or EPS alone[37]. Hyaluronic acid-based hydrogels incorporating PDGF or FGF further improved fibroblast proliferation, collagen deposition, and re-epithelialization. Importantly, the intrinsic antimicrobial properties of EPS reduced bacterial colonization and biofilm formation, creating a favourable environment for tissue regeneration[38]. Advanced EPS-GF systems have also been engineered to respond to wound-specific cues such as pH or protease activity, enabling targeted and controlled growth factor release. Preclinical investigations demonstrate that biomaterial-based growth factor delivery systems significantly accelerate wound closure and improve tissue remodeling compared to conventional treatments[8]. Collectively, these findings confirm that EPS-GF composites provide synergistic antimicrobial and pro-regenerative effects, supporting their potential as next-generation wound dressingsin Table 3.

FUTURE PERSPECTIVES AND CHALLENGES

The EPS-GF composites represent a promising strategy for chronic wound management by integrating the antimicrobial and structural properties of microbial exopolysaccharides (EPS) with the regenerative functions of growth factors (GFs)[3]. Although preclinical studies demonstrate clear therapeutic benefits, several challenges must be addressed to enable clinical translation.

A major limitation is the scalability and standardization of EPS production. Variations in microbial strains, fermentation conditions, and purification processes can affect polymer structure, mechanical properties, and growth factor release behavior[3]. Improved bioprocess control and reproducible modification strategies are therefore essential for clinical-grade EPS manufacturing.

Growth factor stability, cost, and regulatory concerns also remain critical barriers. While EPS matrices enhance GF protection, large-scale use of recombinant proteins raises issues related to immunogenicity, safety, and batch consistency[39]. Strategies such as lower-dose combinations of multiple GFs or the use of more stable engineered analogs may help mitigate these challenges.

Stimuli-responsive EPS-GF hydrogels offer a promising direction, enabling growth factor release in response to wound-specific cues such as pH or enzymatic activity[40]. In addition, multifunctional composites incorporating antimicrobial peptides or nanoparticles may further enhance therapeutic efficacy. Future wound therapies may increasingly rely on microorganism-derived novel bioactive compounds as alternative regenerative and antimicrobial agents[41]. However, clinical validation remains limited, highlighting the need for systematic human trials evaluating safety, dosing, and long-term outcomes.

Overall, advancing EPS-GF composites toward clinical use will require standardized production, cost-effective design, and rigorous clinical evaluation. Addressing these challenges may enable the development of next-generation wound dressings capable of improving outcomes in complex and chronic wounds.

CONCLUSION

Microbial EPS and growth factors (GFs) act synergistically to support chronic wound healing. By merging EPS's antimicrobial and structural support with GFs' angiogenic and regenerative effects, EPS-GF composites tackle the multiple barriers that impair tissue repair. Preclinical studies demonstrate that these composites accelerate wound closure, enhance angiogenesis, promote fibroblast proliferation, and reduce infection risk. The EPS scaffolds can be tailored for physical entrapment, covalent conjugation, or affinity-based binding of growth factors, optimizing release kinetics, preserving protein bioactivity, and supporting cellular infiltration and tissue deposition. This synergy disrupts the chronic wound cycle of inflammation, microbial colonization, and poor vascularization. Future directions include stimuli-responsive hydrogels, multifunctional scaffolds with additional bioactive agents, and scalable, standardized EPS production. Overcoming challenges such as growth factor stability, cost, and clinical translation will be essential. Personalized EPS-GF therapies guided by wound-specific monitoring could further improve healing outcomes. Overall, EPS-GF composites provide antimicrobial protection, sustained growth factor delivery, and extracellular matrix-like structural support, representing a next-generation approach to chronic wound care that can enhance healing, reduce complications, and improve overall patient outcomes.

SIGNIFICANCE STATEMENT

This review highlights microbial exopolysaccharide (EPS)-growth factor (GF) composites as a promising multifunctional strategy for chronic wound healing. By combining the antimicrobial and structural properties of EPS with the regenerative activity of growth factors, these systems enable controlled delivery, enhanced angiogenesis, and improved tissue repair. Overall, EPS-GF platforms offer a next-generation approach to overcome key limitations of conventional wound therapies.

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