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Review

Therapeutics-Loaded Electrospun Nanofibers: Rational Design and Mechanistic Insights on Managing Chronic Wound Infection

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Abstract: Chronic wounds present a multifactorial clinical challenge characterized by prolonged inflammation, microbial biofilm formation, oxidative stress, and impaired vascularization. Conventional wound dressings such as films, hydrogels, and decellularized matrices often fall short due to limited bioactivity, inadequate mechanical properties, and insufficient control over therapeutic delivery. This review highlights electrospun nanofiber membranes as advanced biomimetic platforms that replicate the structural and functional attributes of the extracellular matrix while enabling localized and sustained release of therapeutic agents. The novelty of this work lies in its systematic association of bioactive compounds including antimicrobial, antioxidant, immunomodulatory, oxygen releasing, and hemostatic agents with their specific biological targets in chronic wound healing. Also, the review critically examines fabrication techniques such as coaxial, emulsion, gas assisted, and stimuli responsive electrospinning, and evaluates how key processing parameters influence fiber morphology, drug release profiles, and cellular interactions. By integrating material science with mechanistic insight, this work provides a unified framework for the rational design of responsive nanofiber based wound dressings and outlines future directions involving smart delivery systems, biosensing integration, and three dimensional bioprinting to support clinical translation and personalized therapy. Emphasis is also placed on emerging multifunctional membranes capable of real-time interaction with wound pathophysiology. Challenges related to scalability, regulatory approval, and long-term biocompatibility are discussed to bridge the gap between laboratory findings and clinical adoption. This review ultimately serves as a foundation for developing next generation wound care strategies that are both mechanistically targeted and clinically adaptable.

Keywords: chronic wound infection; electrospinning; delivery of antimicrobial; 3D nanofiber scaffolds; therapeutic agents

1. Introduction

Chronic wounds impose a substantial burden on both the socioeconomic status and the healthcare compliance of patients worldwide [1,2]. Ageing is a significant contributor to the prevalence of chronic wounds; however, individuals with diabetes and obesity face an even higher risk due to factors like hyperglycemia, compromised vascular function, and neuropathy [3,4]. Diabetic-related chronic wounds, such as non-healing ulcers, may even necessitate limb amputation in severe cases [5,6]. These wounds are characterized by a disrupted and prolonged healing process, often complicated by bacterial infections, persistent inflammation, and impaired tissue [6,7].

Chronic wound infections are often polymicrobial, with bacteria such as *Staphylococcus*, *Pseudomonas*, and *Stenotrophomonas* frequently identified (Figure 1) [8]. Bacterial toxins, including endotoxins and exotoxins, provoke immune responses involving immune cells such as neutrophils and macrophages [9,10] Persistently present neutrophils contribute to prolonged pathological inflammation, hindering the healing process [11]. These immune cells also release enzymes that degrade the extracellular matrix, further delaying tissue regeneration and epithelialization [12,13]. In addition to this, several physiological and biochemical barriers further hinder chronic wound healing [14]. Hemostatic dysfunction also plays a critical role, as insufficient clot formation can delay the initiation of the healing cascade [15–17].

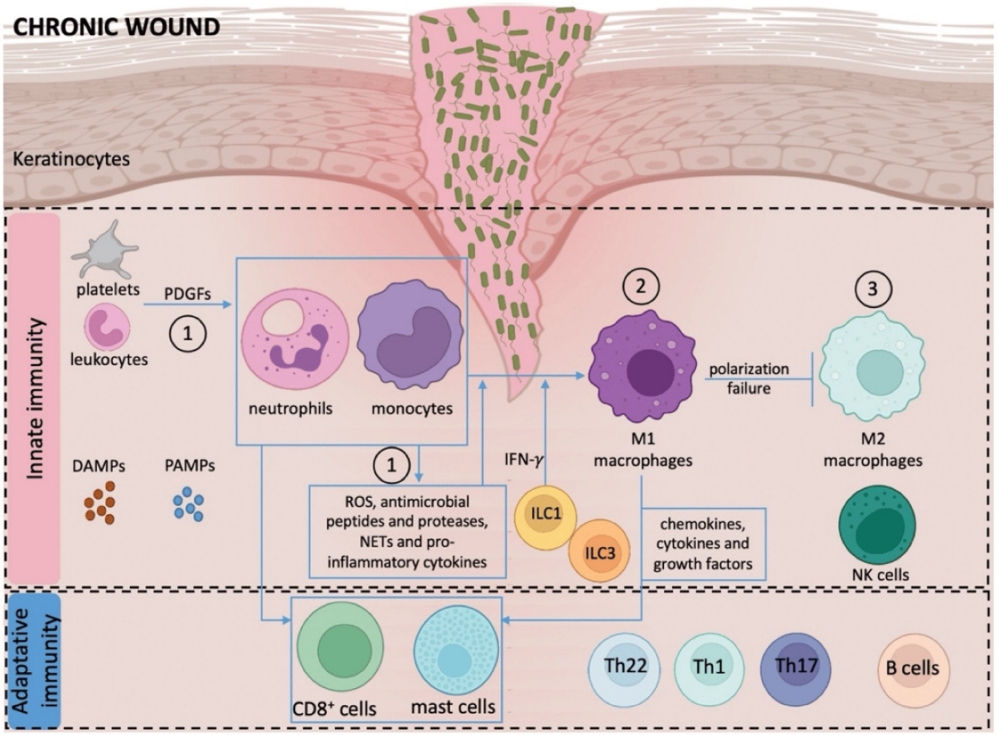

Figure 1. Immune dysregulation in chronic wounds impairs resolution and tissue repair. This schematic illustrates the key innate and adaptive immune mechanisms contributing to the pathophysiology of chronic wounds. Reproduced with permission from Ref. [8]. Copyright 2022, MDPI.

To address these complex pathophysiological barriers, a wide range of wound dressings and biomaterials have been developed [18]. These include thin polymeric films, decellularized extracellular matrix (ECM)-based scaffolds, biopolymeric porous matrices, and hydrogels [7,19,20]. While these materials have demonstrated clinical utility, each possesses inherent limitations. Film dressings often lack sufficient absorbency for high-exudate wounds, decellularized matrices exhibit batch variability and risk of immunogenicity; porous scaffolds may be mechanically weak; and hydrogels, although highly hydrophilic, can lead to wound overhydration and are mechanically fragile [21–23]. These limitations highlight the urgent need for multifunctional, adaptive, and bioactive wound dressings that can address the multifactorial nature of chronic wounds [24,25].

In this review, we critically examine the multifaceted challenges impeding chronic wound healing, including excessive reactive oxygen species (ROS), biofilm formation, dysregulated immune responses, impaired oxygenation, and insufficient hemostasis. We highlight the limitations of current wound dressings such as films, hydrogels, decellularized matrices, and porous scaffolds emphasizing the pressing need for innovative materials capable of addressing these shortcomings. Central to this review is the exploration of therapeutic-loaded electrospun nanofibers, an emerging class of biomaterials that closely mimic the architecture and function of the

natural extracellular matrix while enabling precise, localized, and sustained delivery of bioactive agents. We provide an in-depth analysis of nanofiber systems loaded with antibacterial, immunomodulatory, antioxidant, oxygen-releasing, probiotic, and hemostatic agents, detailing their mechanistic actions in mitigating the chronic wound microenvironment. By systematically comparing these advanced systems with conventional approaches, and by outlining the electrospinning techniques, materials selection, and fabrication parameters that govern their performance, this review offers a unique and integrated perspective on the rational design of multifunctional nanofibrous scaffolds. The novelty of our work lies in its comprehensive mapping of therapeutic mechanisms to specific pathophysiological barriers in chronic wounds, and in presenting a unified framework for the development of next-generation, multifunctional electrospun membranes. This review serves as a timely and valuable resource for researchers and clinicians seeking translational strategies to accelerate wound healing and reduce the global burden of chronic wound infections.

2. Problems Associated with Chronic Wound Infection

Several interconnected factors contribute to the persistence and complexity of chronic wound infections. These pathological elements are summarized in Figure 2 and discussed in the following sections.

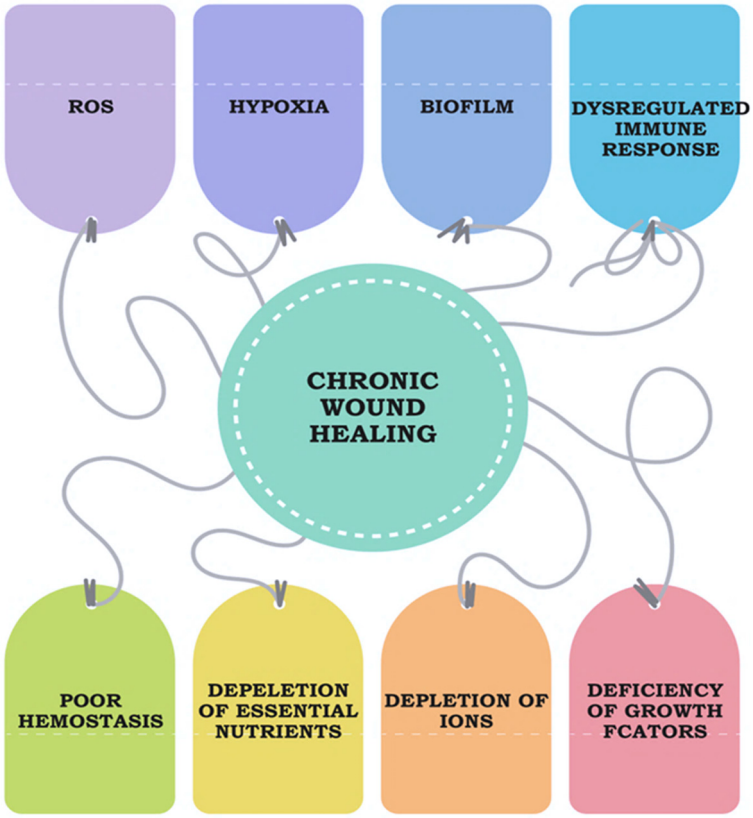

Figure 2. Various factors affecting chronic wounds. This diagram summarizes the interconnected pathological factors contributing to impaired healing in chronic wounds. Key physiological and microenvironmental disruptions include excessive production of reactive oxygen species (ROS), hypoxia, microbial biofilm formation, and a dysregulated immune response.

2.1. Reactive Oxygen Species (ROS)

A major challenge in managing chronic wounds is the elevated presence of reactive oxygen species (ROS) in the wound environment [26]. The key source of cellular ROS production in cells includes mitochondria which generate superoxide (O_2^-) transformed into hydroxyl radicals (•OH) and hydrogen peroxide (H_2O_2) via the electron transport chain [27]. Immune cells such as macrophages and neutrophils also make ROS using NADPH oxidase enzyme, but excess ROS generation can prolong the inflammatory phase. Endothelial cells contain Xanthine oxidase that generates ROS under conditions of ischemia that impair angiogenesis. The generated ROS can lead to peroxidation of lipids, DNA rupture, and oxidation of proteins, leading to impairment of migration of keratinocytes and fibroblasts [28,29].

The excessive production of ROS from different cells, known as respiratory burst, have deleterious effect on the wound healing process. The increased levels of ROS family oxygen derivatives which include hydroxyl radicals, superoxide, hydrogen peroxide, iron as well as copper ions results in oxidative stress triggering damage to the cells [30]. These dysregulations of ROS exacerbate chronic inflammation and disrupt the functionality of vital cellular components, such as endogenous stem cells and immune cells, thereby obstructing the natural tissue repair processes [31]. Compounding the issue, bacterial infections further increase ROS production, causing extensive damage to vascular tissues and endothelial cells, and prolong the wound's chronic nature. The negative impact of ROS on angiogenesis contributes to endothelial dysfunction, thus complicating patient recovery [32,33].

2.2. Impeded Delivery of Oxygen Leading to Hypoxia

The problem of impaired wound healing dynamics is often exacerbated by hypoxia at the wound site, which can be attributed to several factors. Bacteria present in the wound can consume available oxygen, and bacteria-induced cytokines may lead to vasoconstriction, both of which reduce oxygen tension in the affected area [15]. Additionally, the overall oxygen level at the wound site is influenced by blood perfusion, capillary density, and local blood pressure. Despite these challenges, enhancing blood circulation and oxygen supply is crucial for accelerating the healing process. Oxygen is essential for cellular metabolism and other vital cell functions, and maintaining high oxygen tension levels can significantly expedite the healing process [34].

2.3. Biofilm Formation

Biofilm formation is a prevalent factor in most chronic wounds, posing significant challenges to treatment. A biofilm consists of bacteria structured within an exopolysaccharide or exopolymeric substance, adhering to either inert or living surfaces [1]. Approximately 60% of chronic wounds are identified as containing biofilms, which complicates the management of these wounds. Bacteria within biofilms exhibit resistance to both antimicrobial treatments and immune responses, leading to extended healing durations. Once established, biofilms are notoriously difficult to eradicate from wound sites [35]. Moreover, biofilms enhance the likelihood of antimicrobial-resistance gene transfer. This genetic exchange can occur within bacteria of the same species or across different species, escalating the risk for more virulent and persistent infections. The presence of these resistance genes induces genotypic changes in the bacteria, rendering them unresponsive to conventional antibiotics and contributing to recurring infections by antibiotic-resistant bacteria. Consequently, effectively removing biofilm is crucial for promoting wound healing and mitigating the spread of resistant infections [36].

This complex array of issues underscores the urgent need for sophisticated therapeutic approaches in managing chronic wounds. Developing interventions that effectively reduce bacterial infections, control ROS levels, and foster tissue regeneration is critical. Targeted treatments that neutralize excessive ROS can significantly decrease inflammation and bolster the functionality of crucial cellular components involved in tissue repair. Additionally, tackling bacterial challenges within the wound milieu is essential, as these infections can amplify ROS production and further hinder healing. Concurrently, therapies designed to promote angiogenesis and enhance endothelial function are vital to improving nutrient delivery and supporting the comprehensive regeneration of wounded tissue. Together, these strategies aim to establish an optimal environment for wound healing, thus minimizing the prevalence of chronic wounds and enhancing recovery outcomes for patients [37].

2.4. Dysregulated Immune Response

Dysregulated immune responses are major reasons for chronic wound healing as they can lead to an imbalance in the inflammatory response that retards the healing process. The various phases of inflammation, proliferation and remodeling are well-coordinated in a normal wound-healing process. Dysregulation may happen at any stage of healing. The prolonged inflammatory phase leads to the release of pro-inflammatory cytokines such as IL-1 and TNF-α for extended periods, which delays wound healing and regeneration of tissue. Due to the excessive neutrophil activation, reactive oxygen species and proteases will be released that will damage the tissue, preventing wound healing [38,39].

Macrophages are immune cells that are vital for wound healing and they can control both inflammation and proliferation. When these cells become dysfunctional, they either stay in an M1 or pro-inflammatory state or transform into a pro-healing state or M2 state [23].

Immunosuppressed individuals with weakened immune systems can also lead to a delayed healing process. Their immune systems cannot clear pathogens easily as in a normal healing process, leading to impaired therapies. Diabetic people and those who take corticosteroids also face a similar problem [40].

Unnecessary scar and fibrosis formation also contributes to dysregulated immune response, where the balance of repairing tissues and inflammatory signals is poorly monitored. In this case, fibroblast will be over-activated and synthesize large amounts of collagen that causes keloids or scars. Under activation or overactivation of T cells can also lead to such issues [41,42].

2.5. Poor Haemostasis

Hemostasis is the first phase of wound healing and is crucial to prevent bleeding by aggregation of platelets, fibrin clot formation and vasoconstriction. The fibrin clot will act as a momentary matrix, recruiting immune cells to start the inflammatory phase of wound healing [43]. Lack of stable clot formation in chronic wounds will compromise this recruitment delaying inflammation and impairing the healing cascade. Poor hemostasis often leads to bacterial infection complicating the wound [44].

The dysfunction of platelets in chronic wounds will affect the release of platelet-derived growth factor that is essential for blood clotting. Chronic wounds can also arise due to a dysfunctional coagulation cascade. When fibrinolysis increases, more fibrin clots will be broken down by plasmin leading to the unstable formation of clots further worsening the healing process. People with diabetes suffer from vascular abnormalities in which bleeding exceeds and causes insufficient vasoconstriction [18,45]. Medications like antiplatelet or anticoagulants can affect the healing cascade. Vitamin K deficiency can also impair blood clotting. During ageing, platelet function is reduced, clot formation is hindered, and the prevalence of chronic wounds increases. Ongoing blood loss due to poor hemostasis postpends the transition to the subsequent inflammatory phase [46].

2.6. Depletion of Essential Nutrients/Ions

Depletion of ions or essential nutrients can seriously impair wound healing by upsetting numerous physiological processes essential for tissue restoration and renewal. Essential nutrients include proteins, Vitamin C, Vitamin A, Vitamin E, Zinc and iron; whereas essential ions include calcium, magnesium, potassium ions etc. [47,48]. Proteins are essential for immune function, angiogenesis, collagen synthesis and tissue regeneration, whose depletion can lead to decreased proliferation of fibroblasts, impaired immune response, reduced tensile strength and delayed wound healing. Vitamin C, A, E, zinc and iron are required for immune function, antioxidant and collagen synthesis. The deficiency of these can lead to reduced wound strength, weak collagen structures and prolonged healing [17,49]

Essential ions like magnesium, calcium, potassium and magnesium, assist in the synthesis of proteins, migration of cells and blood clotting. Their depletion can lead to reduced tissue repair, poor hemostasis and weakened cellular functions. Topical applications and nutritional supplementation can assist in correcting these deficiencies, enhancing wound healing consequences [50].

2.7. Deficiency of Growth Factors

Deficiency of growth factors disturbs vital processes of wound healing like angiogenesis, tissue repair and cell proliferation. Several growth factors assist in the process. Epidermal growth factor enhances the migration of epithelial cells whose deficiency delays the closure of the wound. Platelet-derived growth factor activates fibroblast and promotes the synthesis of collagen, whose depletion can cause retarded tissue rejuvenation [51]. Vascular endothelial growth factor enhances angiogenesis and deficiency can cause a poor supply of blood. Transforming growth factor-β controls the production of collagen, whose deficiency deteriorates wound structure. Fibroblast growth factor increases the proliferation of fibroblast whose shortage will retard the repair of tissue. Therapeutic interpositions comprise bioengineered materials and topical growth factors to boost healing [52].

3. Current Wound Dressings

3.1. Classification of Current Wound Dressings

3.1.1. Films

Film dressings, characterized by their thin, flexible, and often transparent nature, are crafted from one or more biopolymers. These dressings are permeable to gases and water vapor but act as barriers against liquids and bacteria, safeguarding wounds from moisture loss and external contamination [21]. A primary advantage of film dressings lies in their transparency, which allows for continuous monitoring of the wound-healing process. They also offer the flexibility to incorporate therapeutic agents and can be used as either primary or secondary dressings [25].

The materials typically employed in the production of these dressings include polyurethane, silicone, collagen, chitosan, alginate, and hyaluronic acid. The use of film dressings in medical applications has been established since the early 20th century, leading to a variety of commercially available products [19]. Examples include single-layer films like Bioclusive™ (Johnson & Johnson, New Brunswick, NJ, USA), Tegaderm® Films (3M™, Saint Paul, MN, USA), and Transeal® (DeRoyal, Powell, TN, USA), which predominantly utilize polyurethane, and Simpurity™ films (SafenSimple™, Clarkston, MI, USA) made from silicone. Furthermore, bilayered film options are also available, which generally feature a silicone layer combined with a polysaccharide, protein, or synthetic polymer. This configuration allows the inner layer to meld into the wound bed, delivering therapeutic effects, while the outer silicone layer protects against environmental factors and minimizes water vapor loss. Notable examples include Biobrane® (S&N, London, UK) with its silicone/nylon and collagen composition; Hyalomatrix® (Medline, Northfield, IL, USA), which integrates silicone with hyaluronic acid; and Integra® (Integra LifeSciences Corp., Princeton, NJ, USA), a blend of silicone with collagen and glycosaminoglycan [53,54].

Current research is expanding into new polymeric formulations for films, focusing on enhancing their antimicrobial properties, biocompatibility, biodegradability, and structural integrity. Chitosan, in particular, has gained traction for its potential in developing next-generation film dressings. Innovative products such as Lupeol-loaded chitosan/gelatin films have shown promising antioxidant and antimicrobial activities, along with robust biocompatibility in NIH/3T3 fibroblast studies [10,55]. In a recent study, titanium dioxide nanoparticles (TiO_2 NPs) were successfully embedded into chitosan/poly (vinyl alcohol) (Chi/PVA) films using the casting technique to promote wound healing as shown in Figure 3A. The films demonstrated strong antibacterial efficacy, favorable mechanical and degradation properties, and biocompatibility, including low hemolysis rates. A notable 92.3% wound closure was achieved in vitro within 48 h, highlighting their promise for wound care applications [56].

Ongoing investigations affirm the effectiveness of various polysaccharide-based films in enhancing wound healing, with carboxymethyl cellulose and polyethylene glycol (PEG) films demonstrating notable efficacy in both normal and diabetic wound models. Moreover, protein-based films leveraging fibroin, collagen, gelatin, or soy have been explored for their controlled release capabilities and antimicrobial actions, further boosting their therapeutic value [57,58].

Collectively, these advancements underscore the vital role of film dressings in progressing chronic wound management, offering enhanced protection and promoting healing through the integration of diverse biopolymers and active substances. These innovations represent a significant advancement in the care of chronic wounds, aligning with contemporary medical needs and practices.

3.1.2. Decellularized Matrices

Decellularized matrices, derived from animal or human extracellular matrix (ECM) devoid of cellular components, are gaining traction in the field of chronic wound management. These matrices predominantly consist of natural polymers like collagen and hyaluronic acid, valued for their biocompatibility, bioactivity, and ECM-like properties [59,60].

Collagen, a key ECM component, is crucial in wound healing and tissue repair due to its role in maintaining the ECM's structural and biological integrity. Its dynamic nature allows for continuous remodeling, which is essential for modulating cellular behavior and enhancing tissue functionality. This makes collagen an ideal material for chronic wound dressings, sourced from various origins such as human cadavers, placental tissue, and porcine small intestine submucosa [61]. In a study presented in Figure 3B, researchers developed a mechanically tunable decellularized extracellular matrix (dECM) by optimizing freeze-thaw cycles to preserve its native structure and enhance immune modulation. The modified dECM influenced macrophage behavior through mechanotransduction pathways (cellular signaling routes that convert mechanical stimuli into biochemical signals), promoting M2 polarization and improved tissue regeneration. When tested in a rat skin injury model, the optimized dECM significantly accelerated wound healing, offering a novel strategy for immunomodulatory biomaterials [62].

Among the commercially available decellularized matrices, Oasis® (Healthpoint, Renton, WA, USA), derived from porcine small intestine submucosa and containing a high concentration of collagen type I, also includes proteoglycans and growth factors that improve its biological activity and mitigate the effects of matrix metalloproteinases (MMPs). Graftjacket® (Wright Medical Technology, Memphis, TN, USA), sourced from donated human tissue, maintains essential ECM components like collagen and elastin, creating a scaffold conducive to host cell integration and tissue regeneration. Dermacell® (LifeNet Health, Virginia Beach, VA, USA), processed with MATRACELL® technology, minimizes immunogenicity by effectively removing nucleic acids, thereby enhancing cell proliferation and vascularization [63]. The regulatory environment for these products,

particularly those derived from human sources, involves fewer restrictions under FDA guidelines for human cell, tissue, and cellular and tissue-based products, which simplifies their clinical use.

Placental membranes have been utilized in therapeutic applications for over a century, prized for their dense composition of collagen and growth factors and their lack of human leukocyte antigens, reducing the risk of immunological rejection. These membranes are rich in a suite of biologically active molecules, including MMPs, TIMPs, immunosuppressive factors, and antimicrobial peptides, all of which play pivotal roles in enhancing cellular functions, minimizing rejection, and fostering effective wound healing. The continuing exploration and commercialization of decellularized placental membranes, exemplified by products like Grafix® and NEOX®, as well as active clinical trials, underscore their ongoing importance in advancing wound care strategies [64,65].

3.1.3. Bio-Polymeric Porous Scaffolds

Bio-polymeric porous scaffolds (BPS) are emerging as a superior alternative to acellular naturally derived matrices and cell-based therapies in the management of chronic wounds. They are distinguished by their cost-effectiveness, longevity, and minimal rejection risk. For optimal functionality in wound dressing applications, BPS must meet a variety of specifications, including manufacturability, biodegradability, biocompatibility, appropriate mechanical strength, interconnected porosity, and significant swelling ability, essentially mirroring the human extracellular matrix (ECM) in structure and function [66].

The fabrication of BPS utilizes a diverse array of polymers, from natural sources like proteins, polysaccharides, and proteoglycans, to purely synthetic materials. This versatility is reflected in commercially available products such as Talymed® (Marine Polymer Technologies Inc., Topsfield, MA, USA) and Hyalomatrix® (Anika Therapeutics, Bedford, MA, USA), which are polysaccharide-based, as well as collagen-based scaffolds like Pelnac® (Eurosurgical Ltd., Guildford, UK) and synthetic options like Suprathel® (Surgicorp, Edmonton, AB, Canada) [67,68].

Recent innovations in BPS focus on refining their mechanical and functional characteristics to accelerate healing. This includes the strategic integration of varied cell populations into the scaffold's architecture, utilizing a blend of well-structured polymers like alginate, chitosan, PEG, and polycaprolactone with ECM molecules such as collagen and hyaluronic acid to improve the stability and biocompatibility of these constructs [69]. Advancements in protein-based BPS are particularly notable. In a study, the graphene oxide–collagen–N-acetylcysteine (GO–COL–NAC) scaffold at a concentration of 500 mg/L showed the most effective wound healing, achieving full closure by day 18 in a rat full-thickness skin defect model with significantly higher closure rates ($p < 0.001$). Additionally, a collagen scaffold reinforced with graphene oxide and black phosphorus (COL–GO@BP) shown in Figure 3C exhibited strong near-infrared-induced antibacterial activity and promoted bone regeneration through enhanced biomineralization and activation of the PI3K/Akt signaling pathway. These findings highlight the potential of multifunctional scaffolds for treating complex wounds and infectious bone defects [70].

These examples highlight the potential of combining natural and synthetic polymers to create versatile scaffolds that cater to various aspects of wound healing, thus broadening the scope and efficacy of chronic wound management solutions.

3.1.4. Hydrogels

Hydrogels, with their interconnected and hydrophilic polymeric networks, encapsulate substantial water content, making them an excellent choice for chronic wound dressings since their widespread adoption in the late 1980s [71,72]. These dressings excel in managing dry wounds due to their ability to deliver hydration to the wound bed and sustain a moist healing environment, which is pivotal for effective wound recovery. Furthermore, the inherent cooling effect of hydrogels alleviates pain associated with wound sites [73,74].

Despite these benefits, hydrogels are not without drawbacks, particularly in wounds characterized by heavy exudate. In such cases, hydrogels may contribute to fluid overload at the wound site, increasing the risk of skin maceration and bacterial growth [75]. Unlike more rigid dressing types such as bio-polymeric porous scaffolds (BPS) or films, hydrogels offer the advantage of conformability, moulding to the shape of the wound due to their pliable nature.

Hydrogels are synthesized from a spectrum of polymers, both natural including hyaluronan, fibronectin, chitosan, gelatin, and alginate and synthetic, such as polymethacrylates and polyvinylpyrrolidone (PVP). Market-available hydrogel products such as Aquaflo® (Covidien, Dublin, Ireland), Intrasite Gel® (Smith and Nephew, Andover, MA, USA), Granugel® (Convatec, Flintshire, UK), and Purilon Gel® (Coloplast, Humlebaek, Denmark) exemplify the diversity in hydrogel formulations [76].

Contemporary research underscores the evolution of hydrogels as dynamic platforms for chronic wound management. Studies demonstrate their utility in delivering growth factors, corroborated by promising outcomes

in both rodent models and human trials [77]. A report highlights the development of a zwitterionic hydrogel (DOX@GASGel) composed of gum arabic, acrylic acid, and sulfobetaine methacrylate, designed for effective treatment of infected wounds (Figure 3D). The hydrogel exhibited strong antibacterial activity, eliminating over 99.5% of *S. aureus* and *E. coli*, and showed high antioxidant capacity by reducing reactive oxygen species. In an infected full-thickness wound model in mice, the hydrogel achieved a 97% healing rate by enhancing collagen formation and angiogenesis [78]. More sophisticated, biomimetic hydrogels are now being engineered to emulate physiological conditions. Further exploration has led to hydrogels that house nano-carriers like nanoparticles or DNA plasmids encoding therapeutic agents such as VEGF, enhancing angiogenesis and accelerating wound healing in diabetic models [79,80]. The adaptability of hydrogels to incorporate such diverse functionalities underscores their profound impact on advancing wound care, offering promising avenues for future therapeutic interventions in chronic wound management.

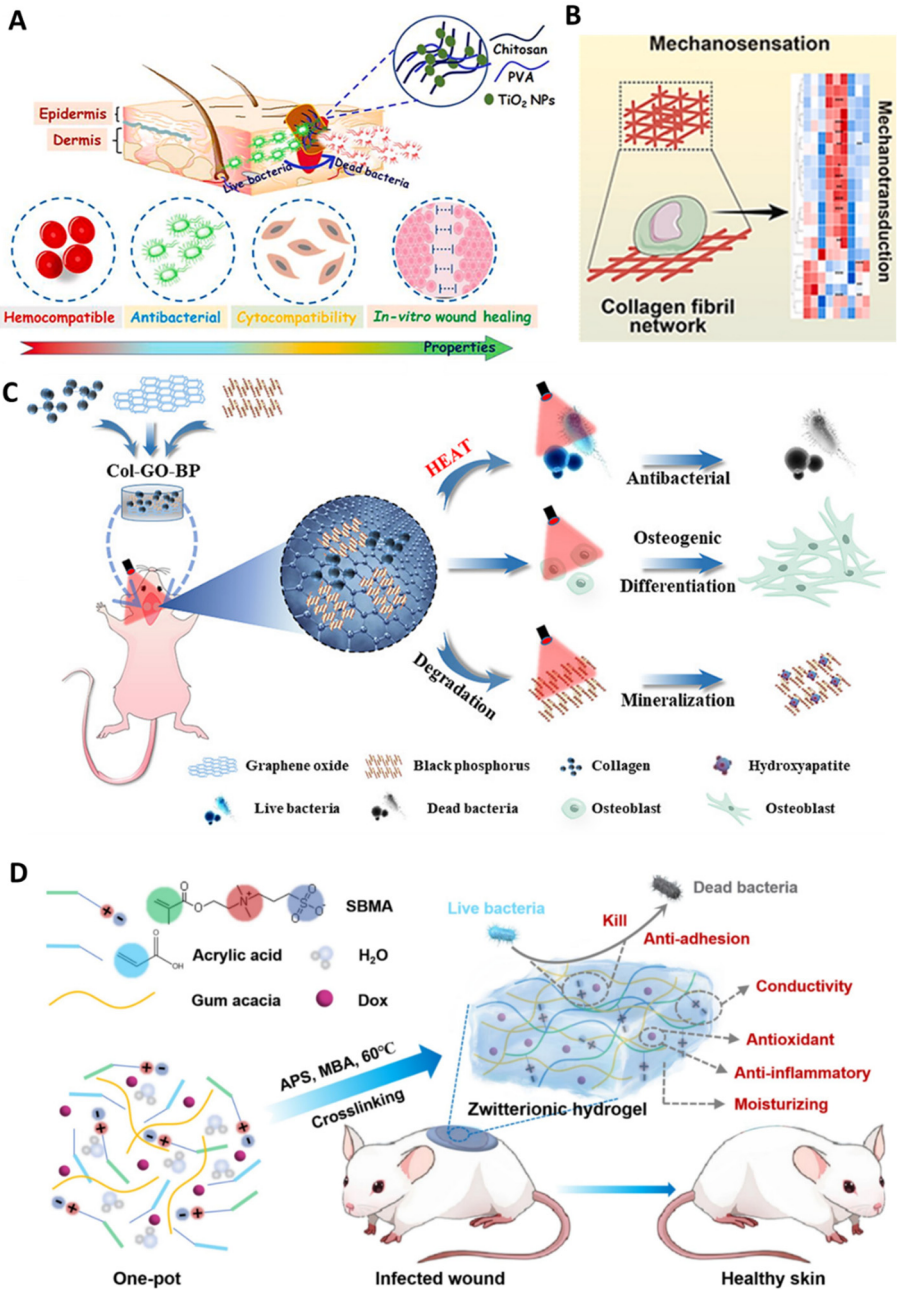

Figure 3. Current common wound dressings and their mechanisms are illustrated as follows: (**A**) A TiO_2-loaded chitosan/PVA film demonstrates strong antibacterial activity and promotes wound healing. Reproduced with permission from Ref. [56]. Copyright 2025, Elsevier. (**B**) Decellularized extracellular matrix highlights collagen-mediated mechanosensation and mechanotransduction, influencing macrophage behavior. Reproduced with permission from Ref. [62]. Copyright 2023, Elsevier. (**C**) GO/BP-functionalized collagen scaffolds that enable NIR-triggered biomineralization and accelerate infectious bone defect repair via activation of the PI3K/Akt

signaling pathway. Reproduced with permission from Ref. [70]. Copyright 2024, American Chemical Society. (**D**) A zwitterionic hydrogel, prepared via a one-pot synthesis, delivers multifunctional benefits including antibacterial, antioxidant, anti-inflammatory, and moisturizing effects. Reproduced with permission from Ref. [78]. Copyright 2025, Elsevier.

3.2. Problems Associated with Current Treatments That Need to Be Encountered

3.2.1. Limitations of Films

Despite the numerous advantages of film dressings, they also present certain limitations that can affect their efficacy in wound management. One of the primary drawbacks is their relatively poor swelling properties, which can lead to the accumulation of excessive wound exudate. This build-up not only hampers the healing process but may also cause discomfort for the patient [81]. While film dressings allow for visual monitoring of the wound, their transparency may compromise protection against UV light, which can be detrimental in some healing scenarios. Additionally, the adhesiveness of film dressings, although beneficial for securing the dressing in place, can cause pain or damage to the skin upon removal, particularly in cases involving sensitive or fragile skin [22]. Overall, while film dressings are highly valued for their protective features and versatility, these limitations must be carefully considered in clinical practice to ensure their appropriate and effective use in managing chronic wounds [20].

3.2.2. Limitations of Decellularized Matrices

While decellularized matrices offer significant benefits in chronic wound management, they also present notable limitations that can impact their practical application. A primary challenge is the variability in quality and consistency, which arises from differences in source materials and decellularization techniques. This variability can lead to unpredictable clinical outcomes, affecting the overall efficacy of these matrices [82].

Despite efforts to minimize immunogenicity, there remains a potential for immune reactions, particularly with xenogeneic matrices that might retain animal-derived components. Such immune responses can complicate the healing process, necessitating rigorous screening and processing to mitigate these risks [83]. The production of decellularized matrices involves complex and costly processes. The steps required to harvest, process, sterilize, and ensure the safety of these products are both resource-intensive and expensive, which may hinder their widespread availability and use in clinical environments [84].

Additionally, the mechanical properties of these matrices pose limitations. While they offer excellent scaffolding for cellular ingrowth and tissue integration, their mechanical strength may not be adequate for high-load applications, restricting their use to scenarios that demand less mechanical support [85]. Lastly, the regulatory landscape for decellularized matrices presents additional hurdles. Each new type of matrix must undergo extensive regulatory scrutiny to confirm its safety and efficacy, a process that is both time-consuming and costly. This stringent regulatory environment can delay the introduction of new matrices into the market, further complicating their adoption in clinical practice [86].

3.2.3. Limitations of Bio-Polymeric Porous Scaffolds

While bio-polymeric porous scaffolds (BPS) hold significant promise for chronic wound management, they are not without their challenges. The variability in degradation rates and mechanical stability of these scaffolds can influence their effectiveness in the dynamic environment of a healing wound. Additionally, despite their inherent biocompatibility, there is still a potential for immunogenic reactions or mild irritation, which can vary based on the patient's sensitivity and the specific polymers used [87].

The manufacturing of BPS, particularly those incorporating sophisticated functionalities like controlled drug release or biosensing, is complex and costly. This complexity can hinder the accessibility and scalability of BPS for broader clinical applications. Achieving uniformity and consistency in BPS properties across production batches remains a significant challenge, essential for ensuring reliable therapeutic effects [88,89].

Moreover, while BPS is designed to enhance cellular interaction and integration, surpassing traditional dressings, they may not provide adequate mechanical protection against external stresses. This inadequacy could compromise the protective barrier needed during the healing process. Additionally, the regulatory landscape for BPS, especially those combining multiple biomaterials to enhance functionality, can be intricate. Navigating this regulatory framework often delays the market introduction of new and innovative BPS products, posing yet another barrier to their widespread adoption in clinical settings [90].

3.2.4. Limitations of Hydrogels

While hydrogels offer significant benefits for chronic wound care due to their high-water content and cooling effects, they also present several limitations that can impact their practical application. The propensity of hydrogels to retain excessive moisture can lead to skin maceration and enhance bacterial growth, especially in wounds with heavy exudate, complicating the healing trajectory. Furthermore, hydrogels often lack the necessary mechanical robustness to provide adequate protection against environmental stressors, limiting their use in wounds requiring substantial mechanical support [91]. The ability of hydrogels to mould to wound contours, while beneficial for coverage, does not compensate for their lack of structural integrity in load-bearing situations. Additionally, their intrinsic high moisture content, while ideal for maintaining a moist wound environment, may not be suitable in conditions where maintaining dryness is crucial, posing a challenge in moisture management [92].

The manufacturing and storage requirements for hydrogels, due to their delicate polymeric nature, can lead to stability issues, affecting their shelf life and effectiveness. Moreover, the cost associated with formulating advanced hydrogels, especially those embedded with bioactive agents for enhanced therapeutic outcomes, can be a barrier, restricting their accessibility in clinical practice. Finally, the regulatory processes required for new medical devices, including innovative hydrogel formulations, can delay their entry into the market, limiting the rapid integration of new therapeutic options into standard care regimes [93].

4. How Nanofiber Can Deal with These Problems

4.1. Optimized Exudate Handling through Porous Architecture

Film dressings often struggle with managing wounds with high exudate due to their poor swelling properties, leading to the risk of maceration and delayed healing. Nanofiber dressings, on the other hand, feature a highly porous structure that excels in fluid management. This capillary-like structure not only absorbs excess fluid but also maintains an optimal moisture level at the wound bed [24]. This balance is critical in promoting autolytic debridement and preventing bacterial growth, both of which are essential for faster wound healing. Moreover, the adaptability of nanofibers allows for the incorporation of hydrophilic materials to further enhance moisture management capabilities, tailoring the dressing to the specific needs of the wound [94].

4.2. Controlled Morphology and Batch Uniformity

Decellularized matrices can vary significantly in quality and consistency due to the biological sources and complex manufacturing processes involved, which also contribute to their high cost. Nanofiber dressings are synthesized through a highly controllable electrospinning process, allowing for precise control over the fiber composition, diameter, orientation, and density. This uniformity ensures consistent product performance, crucial for clinical applications. Additionally, the electrospinning process is scalable and less resource-intensive compared to the production of decellularized matrices, offering a more cost-effective solution while maintaining high-quality standards [95].

4.3. Adjustable Mechanical Properties for Load-Bearing Sites

Bio-polymeric scaffolds may not provide sufficient mechanical strength for wounds subjected to mechanical stress, such as those on joints or areas prone to movement. Nanofiber dressings can be engineered with specific mechanical properties to match or exceed the demands of various wound environments. By adjusting the electrospinning parameters and choosing appropriate polymer blends, manufacturers can produce nanofibers with desired tensile strength, elasticity, and even degradation rates. This customization allows nanofiber dressings to provide robust physical protection and support to the wound area, facilitating the natural healing process without restricting patient mobility [96].

4.4. Moisture Regulation with Structural Stability

While hydrogels are beneficial for their moisture-retaining properties, they often lack the necessary mechanical strength and can over-hydrate the wound. Nanofiber dressings excel in providing a breathable barrier that offers superior moisture control and sufficient mechanical protection [97]. Their network structure mimics the extracellular matrix, supporting efficient gas exchange while preventing fluid build-up. This ensures a protective yet permeable barrier against contaminants, particularly beneficial in protecting the wound from environmental factors and reducing the risk of infection [98].

5. Importance of Nanofiber in Chronic Wound Infection: Biomaterials That Mimic Natural Tissues

Electrospun nanofiber scaffolds offer a remarkable imitation of the natural extracellular matrix (ECM) collagen structure, utilizing a diverse array of natural and synthetic polymers. These scaffolds replicate the native dermal extracellular matrix, boasting a high surface area-to-volume ratio and interconnected porosity, which are ideal for enhancing cellular attachment and growth [96]. Customizable to closely match the tensile strength and elastic modulus of human skin, these scaffolds serve as an excellent platform for targeted drug delivery, aiding significantly in wound healing processes. Additionally, for extensive skin damage, these three-dimensional (3D) scaffolds can effectively serve as substitutes for epidermal grafts [99,100].

When compared to other wound management approaches like hydrogels or sponges, electrospun nanofibers present numerous advantages, particularly in localized drug delivery. Unlike materials such as collagen, fibrin, poly (ethylene glycol) (PEG), and alginate hydrogels which offer soft tissue-like compliance but pose challenges in suturing and lack the strength for physiological loading electrospun nanofibers maintain structural integrity. Furthermore, sponges often encounter issues with the crystallization of hydrophobic active ingredients during encapsulation, leading to a slower dissolution rate and reduced drug effectiveness, which is counterproductive for efficient wound management [101].

Electrospun nanofibers provide abundant structural and functional benefits including promoting hemostasis, high filtration efficiency, semi-permeability, conformability, and scar-free healing, making them highly versatile and effective [102]. The potential for discovering additional benefits of electrospun nanofibers remains vast, suggesting promising avenues for further research and application in medical textiles and beyond [103,104].

6. Techniques to Fabricate Nanofiber Scaffolds

Various fabrication techniques have been developed to produce nanofiber scaffolds with tailored structural and functional properties. Each method offers unique advantages depending on the desired fiber morphology, material compatibility, and application. The Table 1 below summarizes key nanofiber fabrication techniques, highlighting their principles, benefits, and limitations.

Table 1. Various techniques to fabricate nanofiber scaffolds.

Fabrication Techniques	Description	Advantages	Disadvantages	Ref.
Interfacial polymerization	Involves using two different monomers that are soluble in two distinct phases, typically an oil phase and a water phase. Upon dissolution, these monomers undergo polymerization at the interface of an emulsion droplet.	Versatility in polymer types Controlled polymerization Efficient use of materials	Complex setup Limited scalability Dependency on solubility	[105]
Drawing	Similar to dry spinning, is a technique used to produce fibers using a sharp tip or a micropipette, which is a significant advantage due to its simplicity	Simplicity of setup Control over fiber formation Flexibility in fiber arrangement Capability to produce fine fibers with diameters larger than 100 nm Continuous nanofibers can be produced in any arrangement using this method	Scale limitations due to the one-by-one fiber formation approach make it low productivity Material restrictions Size limitations	[106,107]
Spinneret-based tunable engineered parameters (STEP)	Used for forming 3D structures by spinning fibers from nanometers to micrometres in diameter	Highly aligned fibers Versatility in fiber diameters 3D structure formation	Complex equipment requirements Operational challenges Deposition limitations Sensitivity to solution properties	[108,109]

Table 1. *Cont.*

Fabrication Techniques	Description	Advantages	Disadvantages	Ref.
Template synthesis	The use of chemical or electrochemical oxidative polymerization to produce polymeric, metallic, semiconductor, or ceramic nanofibers through a nonporous membrane with numerous cylindrical pores as a template.	Versatility in material production Control over fiber diameter Diverse fiber diameters	Limitation on fiber length Dependence on membrane pore size Process complexity	[110,111]
Phase separation	Utilizes phase separation due to physical incompatibility between components to create nanofibers	Equipment efficiency Customizable mechanical properties Direct fabrication	Limited polymer compatibility No continuous fiber production Gelation challenges	[112,113]
Self-assembly	Is a bottom-up approach to nanomaterial fabrication, where molecules spontaneously organize into predefined structures or patterns through non-covalent forces.	Precision in molecular organization Potential for nanoscale fibers Versatility with molecular units	Complexity and time consuming Low productivity Limited control over fiber dimensions Restriction to specific molecules	[114,115]
Freeze drying	Known as ice segregation-induced self-assembly or solid-liquid phase separation, with three major steps: freezing, primary drying and secondary drying.	Porous structure fabrication No high temperature or leaching steps Biomedical suitability	Complexity in creating hierarchical structures Production limitations	[116]
Electrospinning	A mechanical and electrical technique to fabricate nano-scale fibers using high voltage.	Simple Cost-effective Versatility and adaptability Fabrication of fiber diameter ranging from micrometer to a few nanometer	Low productivity	[117,118]

7. Electrospinning for Fabricating Nanofiber for Chronic Wound Infection

Electrospinning is a versatile technique widely used to fabricate nanoscale fibers, which are ideally suited for numerous applications, including localized drug delivery. This method offers several distinct advantages for incorporating both hydrophilic and hydrophobic active ingredients into nanofiber scaffolds [119]. The simplicity of the procedure allows for seamless integration of drugs without concerns about their hydrophilicity [120]. Moreover, electrospun nanofibers can be engineered to provide controlled drug release, tailored by adjusting the porosity of the fibers and their degradation profiles. Additionally, the technique supports the encapsulation of hydrophobic drug molecules in an amorphous state, which significantly enhances the solubility of the drugs. This combination of features makes electrospun nanofibers an exceptional choice for targeted and efficient drug delivery systems [121].

Electrospinning is a voltage-driven fabrication process that utilizes electric force to draw charged threads of polymer solutions or polymer melts into fine fibers. This technique operates on a simple principle but involves several critical steps to transform a polymer solution into ultrafine fibers. First, a polymer solution or melt is loaded into a syringe, and a high voltage, typically between 15 to 50 kV, is applied. This application of voltage creates a charged liquid droplet at the tip of the syringe. As the electric field strength overcomes the surface tension of the liquid, the droplet elongates into what is known as a Taylor cone (pointed droplet formed under an electric field that initiates fiber jetting in electrospinning) from the tip of this cone, a charged liquid jet is ejected and accelerates towards a grounded collector. During its flight, the solvent in the jet evaporates, culminating in the deposition of ultrafine polymer fibers on the collector. The diameter and morphology of the final fibers are influenced by several

parameters, including the polymer's molecular weight, the viscosity and conductivity of the solution, the flow rate, the strength of the electric field, and the distance between the syringe tip and the collector [122,123].

The ability of the electrospinning process to produce polymer nanofibers with high surface area-to-volume ratios makes it exceptionally useful for a variety of applications. These applications range from filtration and tissue engineering to energy storage, highlighting the versatility and effectiveness of this fabrication technique [124]. There are various types of electrospinning techniques which are used to fabricate therapeutic loaded membranes (Figure 4) [125,126].

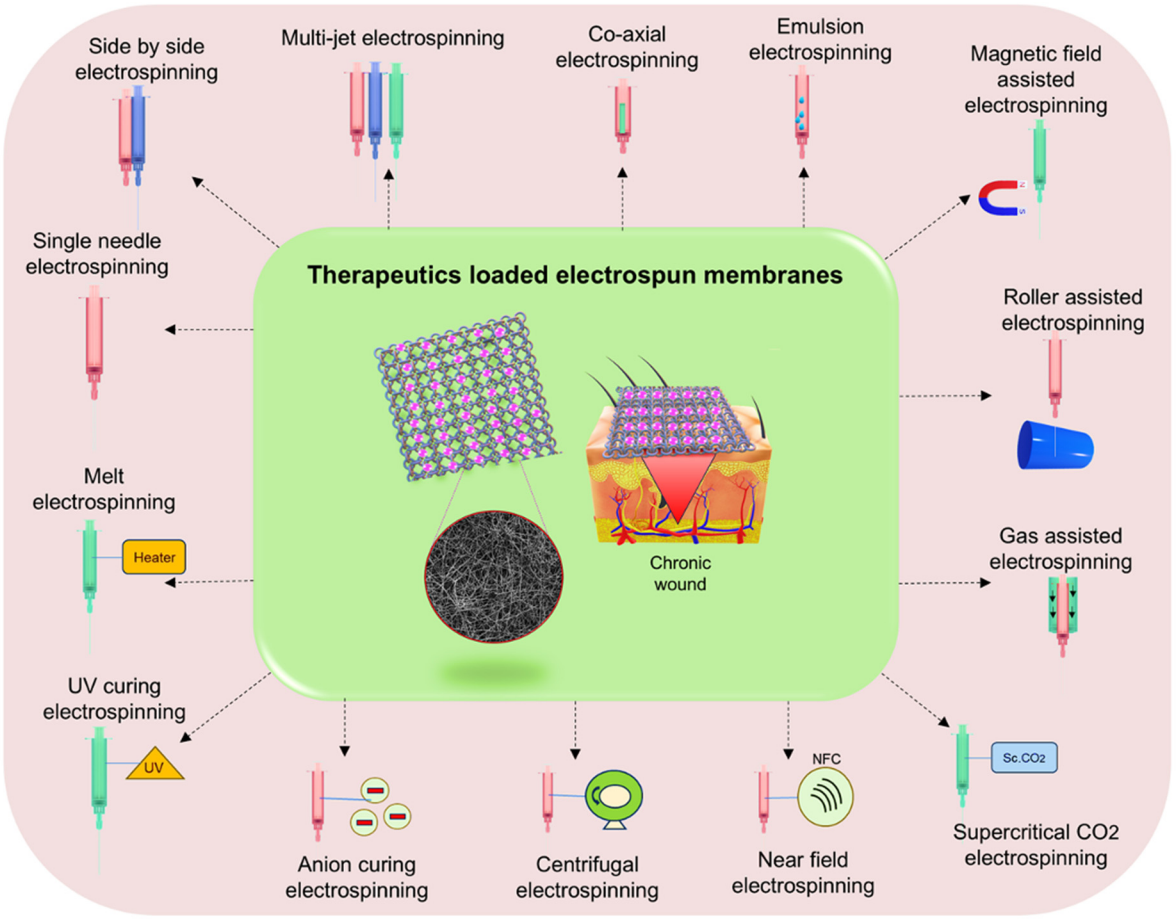

Figure 4. Advanced electrospinning techniques for therapeutic membrane fabrication for chronic wound management. This schematic illustrates various electrospinning technologies employed to fabricate therapeutics-loaded nanofibrous membranes for chronic wound treatment. In the central schematic, electrospun nanofiber scaffolds are shown delivering bioactive agents to a chronic wound site, promoting tissue regeneration and modulating the wound microenvironment.

8. Different types of Electrospinning Techniques

Electrospinning has evolved into a highly versatile platform with numerous variations tailored to specific applications and material systems. The following Table 2 outlines key electrospinning techniques, their operational features, and associated advantages and limitations.

Table 2. Types of electrospinning techniques.

Electrospinning Setup	Description	Advantages	Disadvantages	Ref
Multi-jets from multiple needles	Multiple jets from multiple Taylor cones	• Improve productivity • A simple technique to fabricate composite fibers from polymers that cannot be easily dissolved in common solvents	• Strong repulsion among the jets, thus reduced in fiber production.	[127,128]
Multi-jet from needleless system	Electrically conductive liquid can self-organized into waves at a mesoscopic scale under high voltage, above a critical value, to form jets without the need for needles or capillaries.	• Increased production rate • Improved fiber deposition	• Fiber diameter variation	[129,130]
Coaxial electrospinning	Uses a spinneret with two coaxial capillaries to create core-shell fibers	• Versatility in material use • Enhanced fiber functionality • Precision in fiber structure	• Complex setup • Higher technical demand • Potential for clogging	[131]
Emulsion electrospinning	Combines two immiscible solutions into a single emulsion, which is then electrospun into a fibrous scaffold.	• Dual material capability • Controlled release potential • Use of surfactants and nanoparticles	• Complexity in production • Difficult in fiber formation • Stability requirements	[132,133]
Gas-assisted spinning	Encompasses methods like electro-blowing and melt-blowing, offer a novel approach to spinning materials that traditionally exhibit low electrical conductivity and/or low dielectric constants, which are typically challenging to process using standard electrospinning techniques.	• Enhanced material compatibility • Versatility • Efficient production	• Complex setup • Control challenges • Limited precision in fiber structure	[134,135]
Melt-blowing setup	The polymer jets are then attenuated using high-velocity hot air streams, which significantly reduce the diameter of the jets. The process results in the deposition of a nonwoven web of fine fibers with random orientation on the collector.	• High productivity • No solvent recovery issues • Functional properties	• Polymer limitations • Thermal degradation • Control over fiber dimensions	[136]
Electro-blowing setup	Using polymeric fluid in a straightforward setup, achieving high productivity by spinning long, continuous fibers without the necessity for solvent recovery	• Broad diameter range • High productivity • No solvent recovery • High material efficiency	• Polymer limitations • Thermal degradation • Solvent recovery issues	[137]
Roller electrospinning/ Nanospider electrospinning	Utilizes a roller spinning electrode that is partially immersed in a tank filled with polymer solution, while a grounded electrode moves along with a nonwoven supporting material, facilitating the production of a continuous nanofibro0us layer.	• High productivity • Versatility in material use • Fiber diameter control • Commercial viability	• Solvent recovery issues • Limitations with polymer type	[138,139]

Table 2. *Cont.*

Electrospinning Setup	Description	Advantages	Disadvantages	Ref
Self-bundling electrospinning	The process begins with. Grounded tip wound on a rotating collector to initiate fiber bundle formation.	• Continuous aligned fibers • Simplicity of setup • Control over fiber alignment	• Dependence on electrical conductivity • Initial setup complexity • Scalability issues	[140,141]
Solvent-free electrospinning	Characterized by its absence of conventional solvents, relying instead on alternative methods to convert nearly all the precursor solution into ultrathin fibers.	• Environmental safety • High material efficiency • Diverse techniques	• Technical complexity • Limited material compatibility • Potential for reduced fiber quality	[142,143]
Melt electrospinning	Uses a molten polymer instead of a polymer solution.	• Environmentally friendly • High throughput • Material versatility • Safety features	• High-temperature requirements • Viscosity issues • Fiber quality • Electrical discharge risks	[144]
Supercritical CO_2-assisted electrospinning	Utilize supercritical fluids, such as carbon dioxide, as the solvent medium instead of traditional liquid solvents, and polymer fibers are fabricated using electrostatic forces.	• Solvent efficiency • Innovative approach • Reduced drying time	• Complex equipment needs • Limited collector mobility • Development stage	[145,146]
Anion-curing electrospinning	Enable the transformation of over 90 wt% of the precursor material into ultrathin fibers at room temperature.	• High conversion efficiency • Room temperature processing • Rapid polymerization	• Sensitivity to ambient conditions • Limited material versatility • Potential for rapid curing issues	[147]
UV-curing electrospinning	Modify traditional electrospinning by incorporating UV light to cure the fibers, which requires the oxygen-free environment to prevent the UV curing process.	• Solvent-free process • Efficient fiber formation • Control over curing	• Need for specialized equipment • Limited material compatibility • Dependence on UV exposures	[148,149]
Magnetic-field-assisted electrospinning	An advanced technique that incorporates a magnetic field during the electrospinning process to enhance fiber formation	• Improved fiber uniformity • Smaller fiber diameter • Enhanced fiber alignment	• Complex setup • Material specificity • Operational challenges	[150,151]
Bicomponent spinning	Allows for creating fibers with complex cross-sectional shapes such as side-by-side, islands-in-the-sea, sheath-core, segmented pie, segmented-ribbon, and hollow segmented-pie.	• Versatile fiber design • Multicomponent capability • Structural complexity	• Limited material compatibility • Complex and costly equipment • Specialized process	[152]
Force spinning/ centrifugal spinning	Involves a spinning head that rotates at high speeds, containing the polymer solution or melt; as the spinning head reaches a critical rotational speed, the centrifugal force becomes strong enough to overcome the surface tension of the polymer, ejecting liquid jets from the nozzle tip.	• Enhanced safety • Increased productivity • Material versatility • Reduced production costs • Superior fiber properties	• Dependence on material and design • Complex setup and operation	[153,154]

Table 2. *Cont*.

Electrospinning Setup	Description	Advantages	Disadvantages	Ref
Charge injection method	Utilizes an intense electric field to split the emitted jet rather than accelerating and stretching it.	• Suitable for poor conductors • Unique fiber formation	• Material limitations • Control over fiber size	[155,156]
Near-field electrospinning	A variant of the standard electrospinning process that modifies certain parameters to enhance precision and control in fiber production.	• Reduced needle-to-collector distance • Lower voltage • Volume of deposited fibers	• Risk of electric breakdown • Limitation in material volume • Complex setup for precision	[157]

9. Factors Affecting Electrospun Nanofibers

To achieve optimal results in electrospinning, it is essential to carefully manage a variety of internal and external parameters. Internal factors include the polymer used, solvent, viscosity, and conductivity of the solution. External factors, also known as the process parameters, involve the solution feed rate, applied voltage, the distance between the nozzle and collector, the internal diameter of the nozzle, and the ambient temperature in the chamber [158,159]. Successfully balancing these factors is crucial for producing high-quality electrospun nanofibers.

9.1. The Molecular Weight of the Polymer

The molecular weight of the polymer significantly influences properties such as dielectric strength, surface tension, viscosity, and electrical conductivity of the solution. Polymers with lower molecular weight often led to the formation of beads on the fibers, disrupting the uniformity of nanofiber diameters. Conversely, polymers with excessively high molecular weights can cause the fibers to exhibit high porosity and inconsistent morphology [160,161].

9.2. Viscosity of the Polymer Solution

Polymer concentration is another critical parameter, that directly affects the viscosity and surface tension of the spinning solution. Solutions with low viscosity are prone to producing fibers with defects, typically manifested as beads. Increasing the polymer concentration usually enables a smoother and more continuous fiber extrusion from the nozzle [131,162].

9.3. The Surface Tension of the Polymer Solution

In the process of electrospinning, the Coulomb repulsive forces must overpower the surface tension of the solution to extrude a thin fiber from the Taylor cone. If the surface tension is too high relative to these forces, it can obstruct the jet formation, preventing fiber creation. Optimally, reducing the surface tension allows the process to proceed with lower voltages. While the direct impact of surface tension on fiber morphology isn't conclusively known, it must be sufficiently overcome to draw the polymer solution towards the collector [163].

9.4. The Solvents Used

The choice of solvent is pivotal in determining the success of the nanofibers' fabrication. Solvents that evaporate quickly are typically favored as they affect the solubility of the polymer and active ingredients and expedite the drying process of the nanofibers. Highly volatile solvents are advantageous as they facilitate the quick solidification of fibers, contributing to the creation of a uniform structure with small diameters [164]. Furthermore, solvents are generally selected for their non-hazardous characteristics and FDA approval for biomedical applications, ensuring safety and compliance [165]. The following Table 3, outlines potential solvents used in electrospinning, highlighting their respective advantages and disadvantages to aid in selecting the most appropriate for specific applications.

In practical terms, the solvent system directly influences fiber morphology, drug encapsulation efficiency, porosity, and uniformity, all of which are critical to the performance, safety, and reproducibility of therapeutic nanofiber dressings.

Table 3. Common solvents used in electrospinning with key advantages and limitations.

Solvent	PCL Dissolvable Temperature	Advantages	Disadvantages	Ref
Ethyl Acetate	37–50 °C	Volatile; high electrospinning productivity; thin fiber with a small distribution	Partial solubility; sensitive to temperature change	[102]
Dichloromethane (DCM)	Room temperature	High solubility; high evaporation rate	Toxic, low electrospinning productivity; uneven and high-discrete fibers; porous fibers	[166,167]
Chloroform (CF)	Room temperature	High solubility; high solubility; high evaporation rate	Toxic, low electrospinning productivity; uneven and high-discrete fibers; porous fibers	[168,169]
Ethanol	Room temperature	High evaporation rate	Low solubility;	[170,171]

Table 3. *Cont.*

Solvent	PCL Dissolvable Temperature	Advantages	Disadvantages	Ref
1-methyl-2-pyrrolidone (NMP)	80 °C	High electrospinning productivity; smooth and nanosized fibers; Thin fiber with small distribution.	Partial solubility; Formation of tiny beads.	[102]
N, N-dimethylformamide (DMF)	80 °C	High electrospinning productivity; smooth and nanosized fibers	Partial solubility; Formation of beads and coarse fiber	[172,173]
Dimethyl sulfoxide (DMSO)	80 °C		Slow evaporation rate; insoluble	[168]
Tetrahydrofuran (THF)	40 °C	High solubility;	Low electrospinning productivity; uneven and high-discrete fibers	[174,175]
Formic acid	60 °C		Partial solubility; viscosity and shearing strength may affect the final nanofiber	[174]
Acetone (AC)	50 °C	Low viscosity; high electrospinning productivity; smooth and nanosized fibers; non-toxic	Partial solubility;	[176,177]
Acetic acid	58.8 °C	High solubility;	Partial solubility; viscosity and shearing strength may affect the final nanofiber	[178]

9.5. The Electrical Conductivity of the Solution

The electrical conductivity, when the capillary is charged with a high voltage source, remarkably impacts the jet formation mechanism. The increased conductivity of the solution enhances the charge density, which in turn alters the size of the Taylor cone formed during the process. Studies showed that polymer solutions with low conductivity will result in nanofibers with ideal morphology, while high conductivity solutions will show fiber will be straight [179,180].

10. Therapeutics Loaded Electrospun Membranes for Chronic Wounds and Their Mode of Action

Therapeutics-loaded electrospun membranes provide an innovative and useful tactic for chronic wound management. Figure 5. illustrates the concept of a therapeutics loaded electrospun membrane as a central platform capable of incorporating diverse bioactive agents such as antimicrobials, antioxidants, oxygen, growth factors, and others to synergistically address multiple aspects of chronic wound healing. The tree metaphor symbolizes the membrane's integrative role in supporting and delivering multifunctional therapies for tissue regeneration. Precise engineering of these membranes can result in the controlled release of numerous agents including growth factors, probiotics, antibiotics, immunomodulatory substances, oxygen etc. [181,182]. Their mode of action mainly includes slow degradation of the matrix, releasing the impregnated therapeutics in a slow and controlled process, and guaranteeing steady delivery of drugs over time. The high surface area to volume ratio of these electrospun membranes allows effective interaction with the wound bed and promotes drug delivery [183]. As these membranes are mostly prepared from biodegradable and biocompatible polymers, a moist environment can be created to facilitate tissue regeneration. By averting infections, decreasing inflammation, and enhancing cell growth, these membranes hold great promise in healing chronic wounds [184,185]. Various types of therapeutics-loaded membranes and their mode of action will be discussed in the following sections.

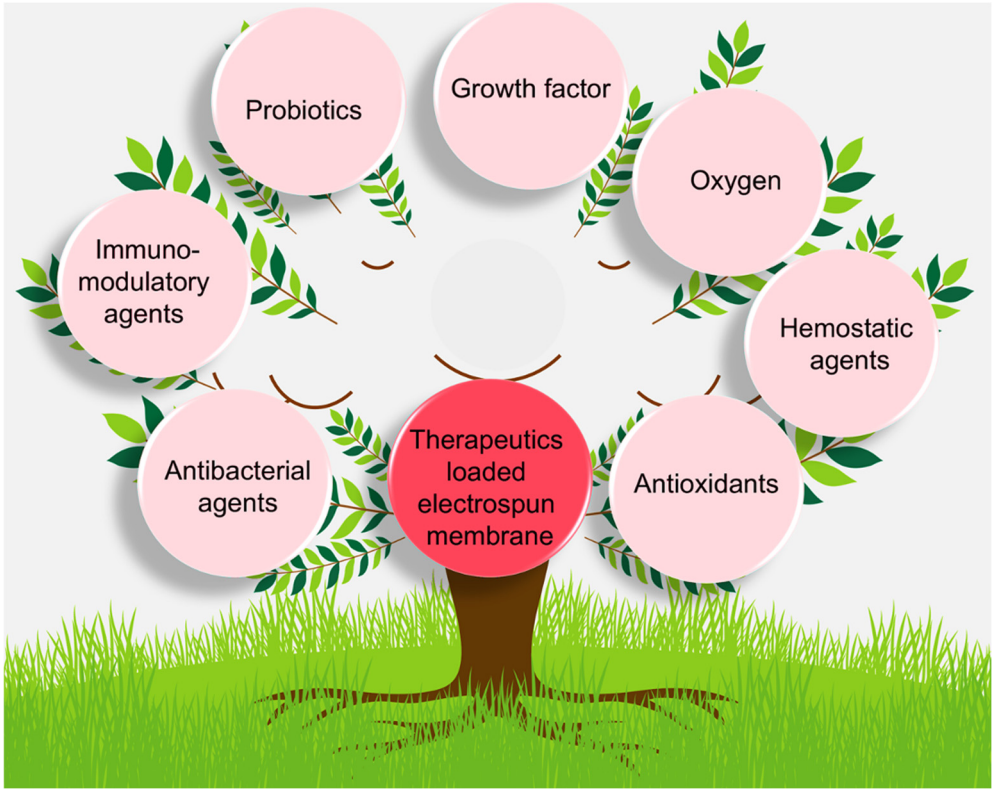

Figure 5. Various therapeutics loaded electrospun membranes. This conceptual illustration represents the multifunctional potential of therapeutics-loaded electrospun membranes in chronic wound management. Depicted as the central trunk of a tree, the electrospun membrane acts as a delivery platform capable of integrating and releasing various classes of therapeutic agents.

10.1. Antibacterial Agents Loaded Electrospun Membranes

Electrospun membranes loaded with antibacterial agents can offer a plausible solution to the issue of chronic wound healing by addressing the problem of bacterial infections. Antibacterial agents include antibiotics (Gentamycin, tetracyclin, amikacin, Ciprofloxacin, Mupirocon etc.); natural antibacterial agents (honey, garlic, curcumin etc.); antibacterial peptides (Cathelicidin and Defensin); nanoparticles (Silver, ZnO, CuO); essential oil (tea tree oil, lavender oil, pomelo oil); polymers (chitosan, Polyhexamethylene Biguanide) and others (iodine, chlorhexidine) [186,187]. The electrospun membranes are engineered to release these antibacterial agents in a slow and sustained fashion for a longer period. This will ensure constant drug concentration at the wound site, which will prevent the development of drug resistance and uphold antibacterial impact for a longer period. In chronic wounds, biofilms are formed by bacteria that protect them from immune responses and traditional treatments. Antibacterial agents dispersed on electrospun membranes can penetrate deeper into these biofilms, damage their structure and make bacteria vulnerable to these agents. By decreasing the colonization of bacteria, the membranes will decrease the inflammatory phase of wound healing giving a favorable environment for tissue regeneration. The fibers will absorb wound exudates and maintain a moist environment for wound healing [188,189].

All these loaded antibacterial agents can disrupt the cell integrity of bacteria through several pathways. For instance, silver nanoparticles get converted to silver ions in solutions that bind to the membrane and cause leakage and destabilization. Essential oils damage the membrane of bacteria by getting into the lipid bilayer. Antibacterial peptides form membrane pores, causing leakage of ions and lysis of cells. Tetracyclin, mupirocin and Gentamicin can target ribosomes, inhibiting the synthesis of functional proteins without which bacteria cannot retain their structure or function. Ciprofloxacin will affect the replication of bacterial DNA constraining topoisomerase and DNA gyrase enzymes, which causes bacterial lysis. Reactive oxygen species are generated by metal oxide nanoparticles that lead to oxidative damage to cell components of bacteria. Lavender oil and curcumin hinder enzymes regulating biochemical pathways, preventing the growth of bacteria [190]. In a report PVA/chitosan electrospun membranes loaded with CuO NP were developed, showcasing improved biocompatibility, antimicrobial properties and thermal stability. In vivo studies confirmed the healing of wounds in 12 days. Another group fabricated PVP/PVA-based coaxial electrospun membrane impregnated with Ag-doped hydroxyapatite

nanoparticles which exhibited high hydrophilicity, sustained drug release, and cell viability. The antibacterial effects and wound healing efficacy were confirmed in vivo (Figure 6) [159].

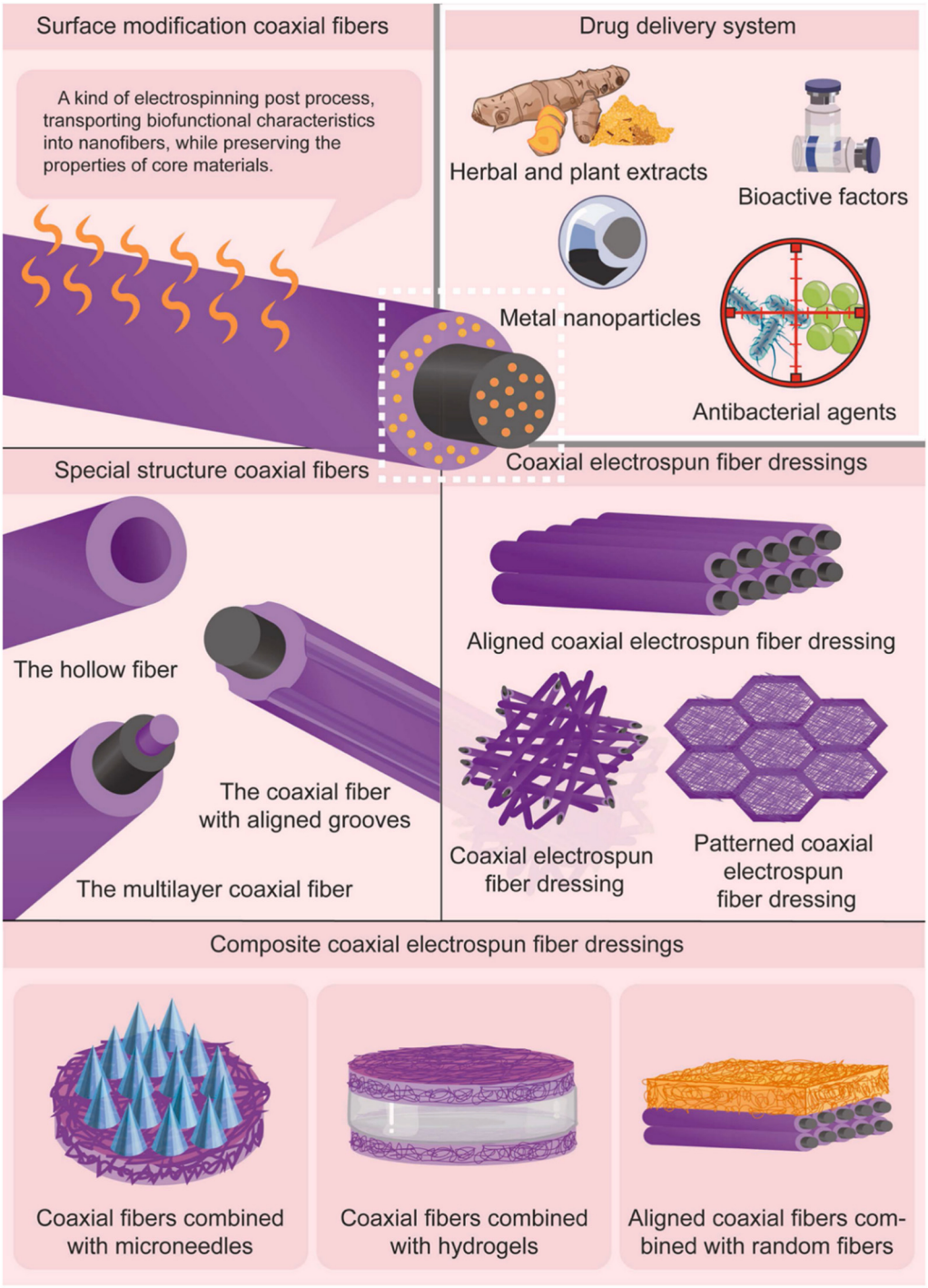

Figure 6. Co-axial electrospun membranes loaded with antibacterial agents such as curcumin, metal nanoparticles or bioactive factors and their recent trends in wound management. This schematic illustrates the multifunctionality of coaxial electrospun fibers tailored for advanced wound care. Coaxial fibers can be surface-modified post-electrospinning to impart bioactivity while preserving core properties and serve as delivery systems for diverse therapeutic agents, including herbal extracts, metal nanoparticles, bioactive factors, and antibacterial compounds. Reproduced with permission from Ref. [159]. Copyright 2024, Elsevier.

10.2. Immunomodulatory Agents Loaded Electrospun Membranes

Electrospun membranes integrated with immunomodulatory agents are another novel strategy for controlling chronic wound healing by influencing local inflammatory response. A prolonged inflammatory phase is observed in the case of chronic wounds [191]. The incorporated immunomodulatory agents can target the local immune

milieu to enable advance through the essential stages of healing. Various immunomodulatory agents include cytokines (IL-4, IL-10, TNF-α, IFN-γ), growth factors, drugs (dexamethasone, ibuprofen), nanoparticles (AuNP, AgNP), microparticles, natural extracts (chitosan, aloe vera, curcumin), anti-inflammatory peptides etc. [192].

In chronic wounds, there is excessive production of pro-inflammatory cytokines like IL-6, IL-1β etc. By incorporating anti-inflammatory cytokines (IL-10) or corticosteroid drugs, this immune response can be suppressed, decreasing damage to tissues and resolving inflammation issues. Interferones such as IFN-γ can promote the surveillance of immune cells and activation of macrophages to boost immune response. The modes of action of various inflammatory drugs are diverse [193]. For instance, Dexamethasone can suppress the release of pro-inflammatory cytokines and obstruct the activation of immune cells, decreasing inflammation. Curcumin acts by inhibiting nuclear factor-kappa B and other signaling pathways causing inflammation. The cyclooxygenase enzymes are inhibited by Ibuprofen to induce anti-inflammatory effects. Anti-inflammatory peptides can block the major inflammatory signaling pathways including NF-κB to decrease inflammation. By transporting agents that can control cytokine profiles, electrospun membranes can switch the inadequate release of growth factors and chemokines. This assists in recruiting essential cells like keratinocytes and fibroblasts while averting unnecessary migration of immune cells, thus regulating the immune response [194,195].

Immunomodulatory agents can dictate the inflammatory and proliferative phase of healing, by shifting macrophages from the M1 phenotype (pro-inflammatory) to the M2 phenotype (anti-inflammatory) by secreting VEGF and TGF-β that promote angiogenesis and tissue repair. AuNP can modulate the polarization of macrophages, enhancing anti-inflammatory M2 phenotype and decreasing oxidative stress. Chitosan also activates macrophages, modulates the production of cytokines, exhibits antibacterial properties and promotes wound healing [196].

Ju et al., have fabricated polyurethane nanofibers-based wound dressing loaded with silver nanoparticles and Chinese medicinal extracts (*Resina Draconis* and *Rhodiola rosea L.*) to enhance diabetic wound healing and reduce inflammation (Figure 7) [197].

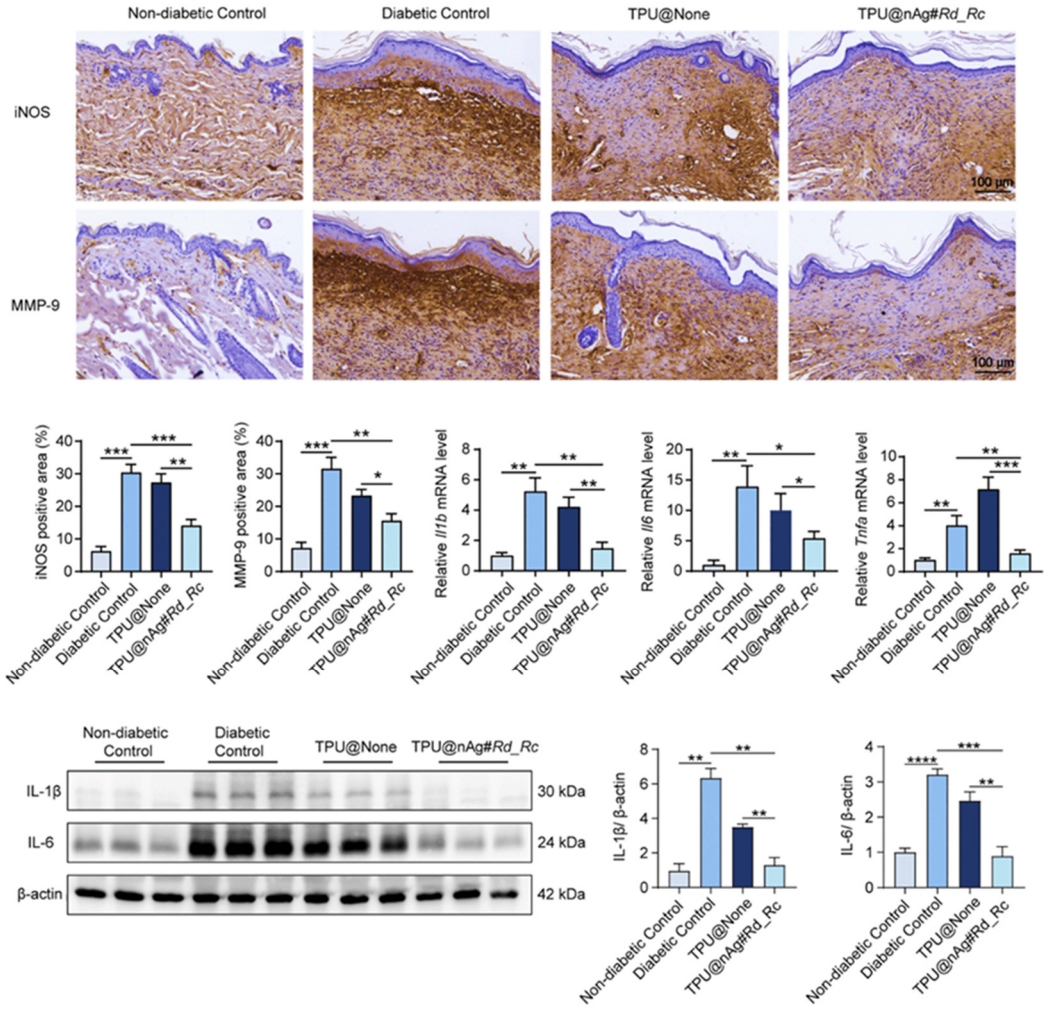

Figure 7. Immunomodulatory effects of electrospun membranes evaluated via histological and molecular analyses. This figure demonstrates the anti-inflammatory efficacy of electrospun polyurethane nanofiber membranes loaded

with silver nanoparticles and Chinese medicinal extracts—Resina Draconis and *Rhodiola rosea* L. (TPU@nAg#Rd_Rc)—as developed by Ju et al. for diabetic wound management. Reproduced with permission from Ref. [197]. Copyright 2024, Royal Society Of Chemistry. Immunohistochemical staining of iNOS and MMP-9 in wound tissues shows a marked reduction in pro-inflammatory markers in the treated group compared to diabetic controls. Quantitative analysis confirms significantly decreased iNOS and MMP-9 positive areas. Corresponding mRNA expression levels of pro-inflammatory cytokines (*Il1b*, *Il6*, *Tnfa*) are also downregulated in the TPU@nAg#Rd_Rc group. Western blot analysis further reveals reduced IL-1β and IL-6 protein levels. These results collectively indicate that the TPU@nAg#Rd_Rc electrospun membrane effectively modulates inflammation, restores immune balance, and promotes improved healing outcomes in diabetic wounds. Statistical significance is indicated as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

10.3. Oxygen-Loaded Electrospun Membranes

Hypoxia is a major issue faced in wound healing which can be addressed using oxygen-loaded electrospun membranes [198]. Oxygen depletion or hypoxia can affect the healing process by decreasing the proliferation of cells, formation of extracellular matrix and angiogenesis (Figure 8A) [199]. Such electrospun membranes can provide oxygen directly to the site of the wound, thereby promoting the regeneration of tissue by increasing oxygenation in the wound bed. Sources of oxygen include peroxides (magnesium peroxide, hydrogen peroxide, calcium peroxide etc.), hemoglobin, myoglobin, nanoparticles, microbubble-based systems, hydrogel layers infused with oxygen and encapsulated liquid oxygen. Peroxides undergo hydrolysis and release oxygen when they react with water. Catalase enzymes can hydrolyze hydrogen peroxide to water and oxygen [200]. Some nanoparticles like cerium oxide nanoparticles can catalyze such hydrolytic reactions and assist in the release of oxygen. Myoglobin or hemoglobin acts as a carrier by binding oxygen and releasing it at needed sites based on the difference in partial pressure of oxygen. Encapsulation of oxygen within microbubbles is another technique which releases oxygen when bubbles collapse [201]. Hydrogel electrospun membranes infused with oxygen can release oxygen as hydrogel degrades. Gas-permeable membranes or silica-based membranes permit easy oxygen diffusion and enhance wound healing. Each of these strategies aims to release oxygen to tissues suffering from hypoxia and promote wound healing [16].

Sustained oxygen release from electrospun membranes including solid-state oxygen carriers, perfluorocarbon-based compounds will release oxygen as the membrane slowly degrades and intermingle with the wound web. Increased oxygen supply will help in the formation of blood vessels which are important for providing nutrients and waste removal from the site of a wound. Oxygen will also aid in the migration and proliferation of keratinocytes and fibroblasts, major cells in wound closure and new tissue formation. Increased oxygenation can also decrease the chronic inflammatory condition by pro-inflammatory cytokine downregulation and enhancing the transition to the proliferative phase. Enhanced oxygen supply will make it less favorable for anaerobic bacteria to survive at the wound site [202].

A study focused on the use of fluorinated zeolite particles embedded within polycarbonate urethane scaffolds that acted as oxygen carriers, increasing oxygen delivery to smooth muscle cells [203]. Microalgae are another interesting oxygen-generating microorganism that can be incorporated within electrospun membranes to protect cells suffering from hypoxia. They undergo photosynthesis and liberate oxygen beneficial for hypoxic cells (Figure 8B) [204].

10.4. Hemostatic Agents-Loaded Electrospun Membranes

To address issues related to blood clotting and manage chronic wounds, electrospun membranes can be impregnated with hemostatic agents. Engineering of these membranes can facilitate the delivery of hemostatic agents at the site of injury facilitating localized and instant action to regulate bleeding [205]. The highly porous architecture of electrospun membranes will allow quick absorption of wound exudates enhancing faster hemostasis. The different hemostatic agents include proteins (fibrinogen, collagen), polysaccharides (chitosan, oxidized cellulose), inorganic agents (zeolites, kaolin), synthetic polymers (polyvinyl alcohol, polyethylene glycol), enzymes (thrombin), platelet-rich plasma, biological extracts like gelatin etc. Fibrinogen, chitosan and thrombin can accelerate the coagulation cascade, creating a stable clot to halt bleeding rapidly [206,207].

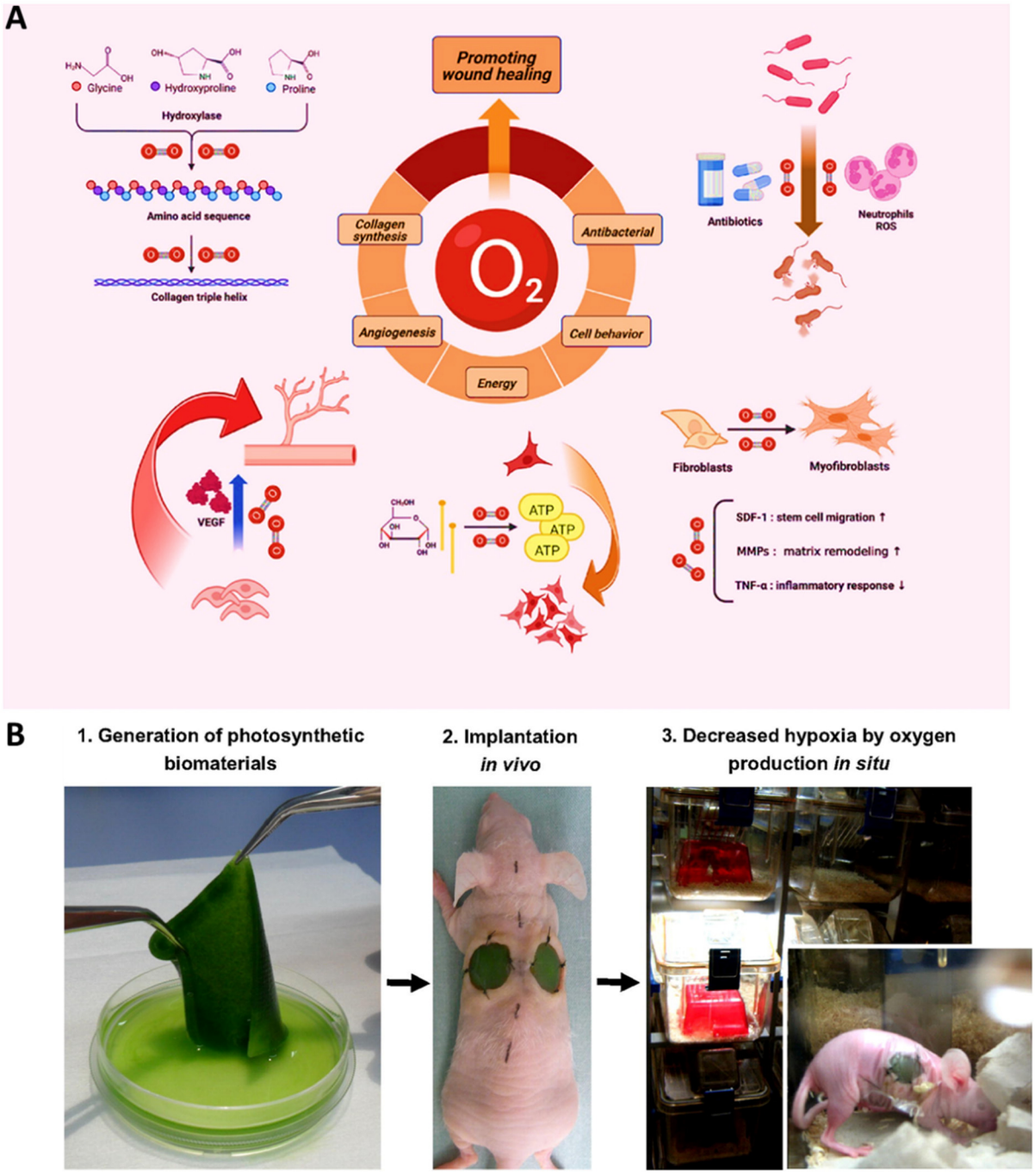

Figure 8. Enhancing wound healing through oxygenation and photosynthetic biomaterials. (**A**) Schematic illustration of the multifaceted role of oxygen (O_2) in promoting wound healing. Oxygen supports collagen synthesis, angiogenesis (via VEGF upregulation), cellular energy production (ATP synthesis), fibroblast proliferation, and myofibroblast differentiation. It also enhances antibacterial defense and modulates inflammatory responses by regulating matrix remodeling enzymes (MMPs), stem cell recruitment (SDF-1), and pro-inflammatory cytokines (e.g., TNF-α). Reproduced with permission from Ref. [199]. Copyright 2023, Elsevier. (**B**) To address hypoxia in chronic wounds, photosynthetic biomaterials were developed using living photosynthetic organisms and implanted in vivo. These biomaterials generate oxygen in situ, significantly alleviating local hypoxia, enhancing tissue oxygenation, and accelerating the wound healing process. Reproduced with permission from Ref. [204]. Copyright 2015, Elsevier.

The positively charged chitosan can attract negatively charged red blood cells forming a clot. Chitosan can enhance adhesion and aggregation of platelets and cause vasocontriction locally which decreases the flow of blood to the wound area. The acidic pH of oxidized cellulose enables it to denature blood proteins enhancing the clotting process. On the other hand, fibrinogen converts to fibrin in contact with thrombin, polymerizing and forming mesh trapping red blood cells and platelets and forming a stable clot. Collagen and kaolin can activate the intrinsic signaling pathway of coagulation, activating Factor XII and leading to the formation of thrombin and clots. Zeolites can concentrate the blood by absorbing water as well as activating Coagulation factors. PEG and PVA can crosslink to form hydrogels preventing further flow of blood. Platelet-rich Plasma Delivers concentrated clotting factors and growth factors that increase the aggregation of platelets and activation, hastening the normal coagulation and tissue reparation. Absorption of blood is possible in the case of gelatin, which swells and prevents bleeding by acting as a barrier [208–210]. Nano clay-containing electrospun membranes made from polyvinylpyrrolidone showed quicker hemostatic performance both in vivo and in vitro (Figure 9A) [211]. Nanofibrous membranes made of polyethylene oxide and thrombin can clot blood in vivo and are promising materials. Hemostasis will be faster if the incorporated moieties can eradicate bacteria or modulate inflammation as all these phenomena are well connected [212]. In another study, electrospun poly (L-lactic acid) (PLLA) nanofiber mats were developed incorporating aluminum chloride (hemostatic), gentamicin sulphate (antibiotic), and lidocaine hydrochloride (anesthetic). The $AlCl_3$-loaded mats showed optimal hemostatic performance, reducing clotting time by 80% and enhancing blood absorption by 178% compared to gauze. Drug release analysis revealed that gentamicin followed Korsmeyer–Peppas kinetics with a high correlation (R^2 = 0.999, n = 0.1), indicating controlled release behavior (Figure 9B) [213].

10.5. Antioxidants-Loaded Electrospun Membranes

An advanced strategy in chronic wound management is electrospun membranes loaded with anti-oxidants that can reduce oxidative stress, responsible for delaying healing (Figure 10A) [214]. Venous ulcers, diabetic ulcers, and pressure sores are chronic wounds that have an imbalance between ROS production and the wound's potential to deactivate them., causing a lengthy inflammatory phase [215]. Antioxidants can scavenge ROS, balancing immune response and promoting tissue regeneration. Antioxidants include curcumin, tocopherol, ascorbic acid, resveratrol, glutathione, ubiquinone, polyphenol, N-acetylcysteine, selenium, melatonin etc. The electrospun matrix slowly degrades, releases antioxidants and provides localized protection against oxidative stress [216].

Tocopherol acts by donating hydrogen atoms to lipid radicals, avoiding peroxidation of lipids in the cell membranes. It can shield cell membrane integrity by preventing oxidative damage and decreasing the release of pro-inflammatory cytokines, supporting immune response [217].

Ascorbic acid can neutralize ROS, and promote the synthesis of collagen by acting as a co-factor for enzymes that assist in crosslinking collagen fibers and provide immune support [218]. Curcumin acts by neutralizing ROS, inhibiting NF-κβ, decreasing inflammation and promoting blood vessel formation. Resveratrol activates superoxide dismutase (antioxidant enzyme), scavenges free radicals, inhibits NF-κβ and promotes angiogenesis [219]. Glutathione can reduce hydrogen peroxide to alcohol and water, assists in the regeneration of Ascorbic acid and is involved in the detoxification of the wound site. The mode of action of Coenzyme Q 10 involves neutralizing free radicals, decreasing oxidative damage, increasing energy (ATP) production and reducing inflammation by modulation of pathways of inflammation. Polyphenols can enhance superoxide dismutase, scavenge free radicals and decrease oxidative stress. Selenium can act as co-factors of antioxidant enzymes, decrease oxidative stress, and enhance immune activity. Melatonin scavenges ROS, enhances superoxide dismutase and protects mitochondria and other organelles from oxidative stress [220,221].

Wang et al. have constructed an antioxidant defence system made of electrospun members of Pluronic F127, styrene-b-(ethylene-co-butylene)-b-styrene elastomer, 1,2-ethanedithiol and poly (ethylene glycol) diacrylate and antioxidants such as ascorbic acid, pro drog named as AA-2G. These bioinspired membranes decreased oxidative and mechanical damage to cells and upheld the normal ROS level required by the body (Figure 10B,C) [222].

In a nutshell, antioxidant-loaded electrospun membranes help in chronic wound modulation by scavenging ROS, promoting wound healing, overcome oxidative stress. The sustained release of antioxidants provided a targeted method for overcoming oxidative stress, a major cause of serious wound pathogenesis.

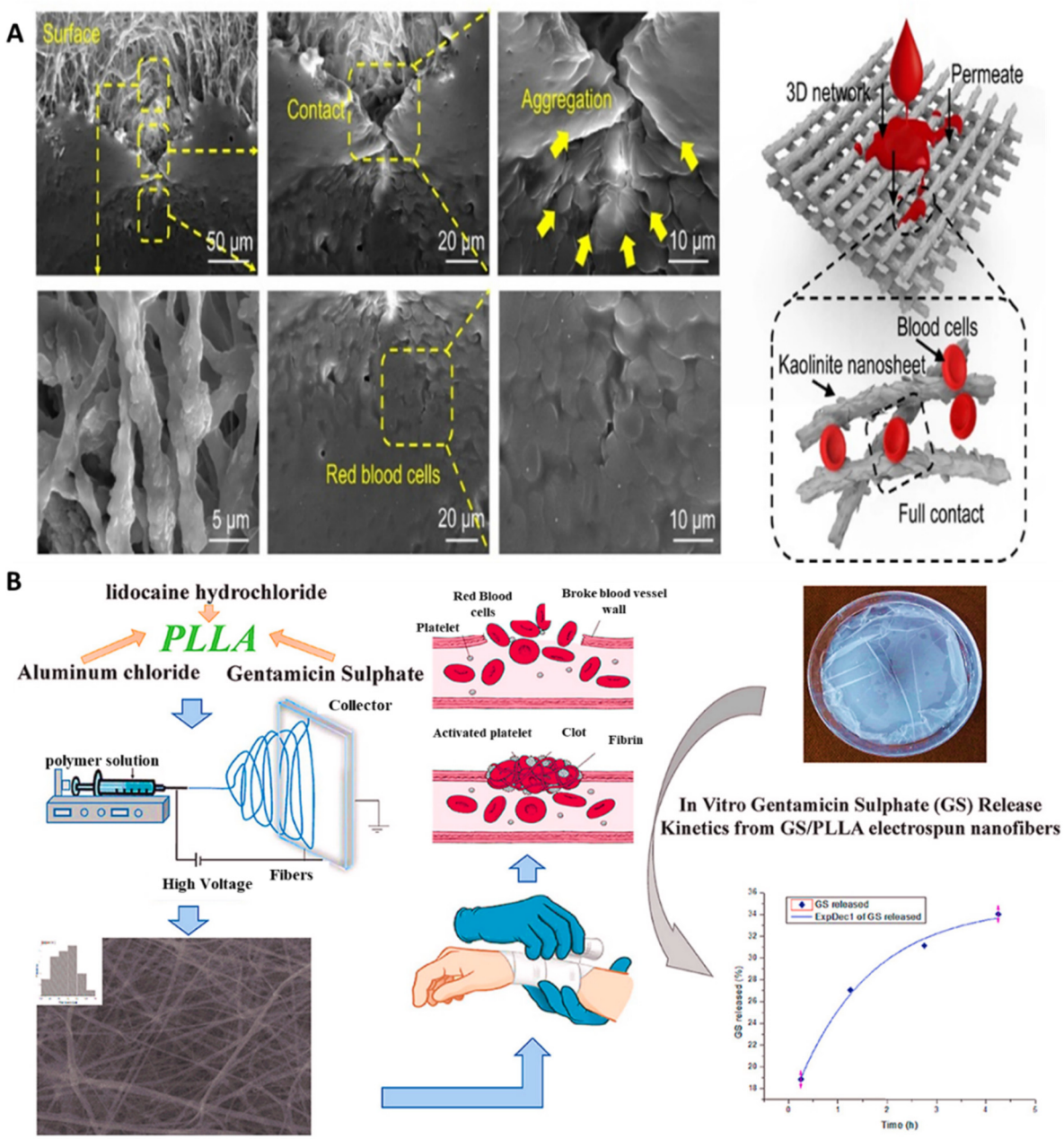

Figure 9. Hemostatic and antibacterial electrospun nanofibers for wound healing applications. (**A**) Scanning electron microscopy (SEM) images of electrospun membranes impregnated with nanoclay, demonstrating their fibrous architecture and surface roughness conducive to clot formation. The proposed mechanism of hemostasis involves nanoclay-mediated activation of the intrinsic coagulation cascade, promoting rapid blood absorption and clot stabilization. Reproduced with permission from Ref. [211]. Copyright 2022, Elsevier. (**B**) Schematic illustration of a multifunctional electrospun poly(L-lactic acid) (PLLA) nanofiber system co-loaded with gentamicin (antibacterial agent), lidocaine (local anesthetic), and aluminum chloride (hemostatic agent). This composite nanofiber platform is designed to simultaneously provide infection control, pain relief, and rapid hemostasis, thereby accelerating wound healing in acute and chronic settings. Reproduced with permission from Ref. [213]. Copyright 2021, Elsevier.

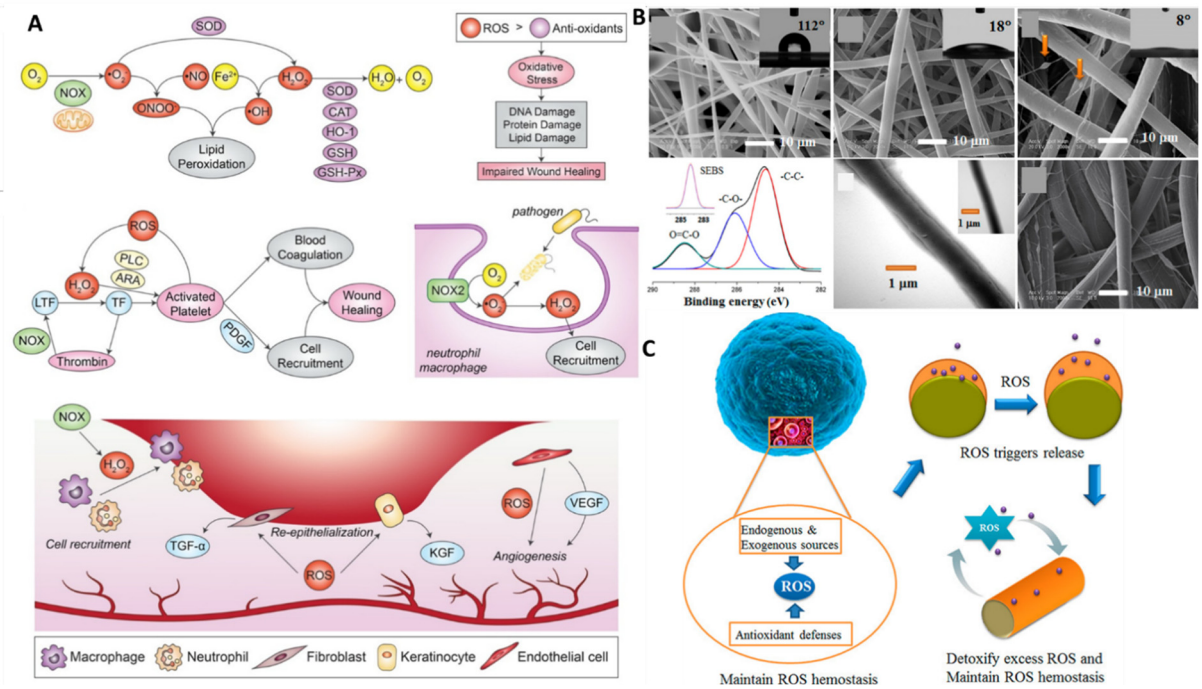

Figure 10. Role of reactive oxygen species (ROS) and antioxidant-loaded electrospun membranes in wound healing. (**A**) ROS are key regulators in wound healing, involved in lipid peroxidation, blood coagulation, cell recruitment, and angiogenesis. While physiological levels of ROS promote tissue regeneration through TGF-α, KGF, and VEGF signaling, excessive ROS causes oxidative stress, damaging cellular components and impairing healing. Reproduced with permission from Ref. [214]. Copyright 2023, MDPI. (**B**) SEM and XPS analyses of antioxidant-loaded electrospun membranes show nanoscale fiber morphology, surface chemical composition, and enhanced wettability—features beneficial for cellular interaction and wound repair. (**C**) Schematic representation of antioxidant-loaded systems that respond to elevated ROS levels by releasing therapeutic agents. These systems help detoxify excess ROS and restore redox balance, thus maintaining ROS homeostasis critical for proper wound regeneration. Reproduced with permission from Ref. [222]. Copyright 2017, American Chemical Society.

10.6. Probiotics-Loaded Electrospun Membranes

Electrospun membranes impregnated with probiotics present a novel approach to modulating chronic wounds by making use of the potential benefits of probiotics to enhance healing and decrease infection. These membranes release live bacteria or 'good bacteria' at the site of the wound. There is an imbalance in wound microbiota in the case of chronic wounds with an exceeded level of pathogenic bacteria compared to beneficial bacteria (Figure 11A) [223]. Lactobacillus or Bifidobacterium probiotic species restore the normal balance of microbes by outcompeting destructive bacteria, eradicating infection and favoring an improved wound environment [224]. The local immune response is modulated by probiotics at the site of the wound by incating with the immune cells of the host. They suppress the release of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines, decreasing chronic inflammation. The barrier function of the skin is increased using probiotics by promoting epithelization, creating a protective layer and eradicating an invasion of bacteria [225]. This barrier layer is vital for chronic wound healing which faces issues of long-lasting attack by bacteria. Probiotics can secrete factors that enhance angiogenesis and promote the regeneration of tissue. These effects are important for chronic wounds suffering from insufficient blood circulation and supply of nutrients, that promote quicker repair of tissues. Antimicrobial peptides secreted by probiotics can kill bacteria like *Staphylococcus aureus* and *Pseudomonas aeruginosa*, typical bacteria found at wound sites. They can also produce antioxidants and reduce oxidative stress. Lactosporin-loaded electrospun membranes exhibited antibacterial properties against a wide number of bacteria and are used as wound dressing patches. Probiotic (*Enterococcus mundtii*) functionalized electrospun nanocomposite scaffolds made of poly(vinyl alcohol), glycerol and poly(vinylpyrrolidone) can control infection and enhance skin burn healing in Balb/c mice models [226]. In a study, electrospun nanocomposite scaffolds containing the probiotic *Enterococcus mundtii* were developed using poly (vinyl alcohol), poly(vinylpyrrolidone), and glycerol. These bio scaffolds enhanced probiotic viability, degraded in wound-like environments, and effectively suppressed pathogenic bacteria. In a murine burn model, the probiotic-loaded scaffolds significantly improved wound healing by promoting tissue regeneration and reducing infection (Figure 11B) [227].

The controlled release of probiotics ensures therapeutic dosage of good bacteria is carried unceasingly to the injury site as time passes by. The electrospun membrane facilitates direct contact between the wound site and probiotics, confirming that the good bacteria are delivered exactly where they are desired. These provide biocompatible approaches for managing venous leg ulcers, diabetic ulcers and pressure ulcers [228,229].

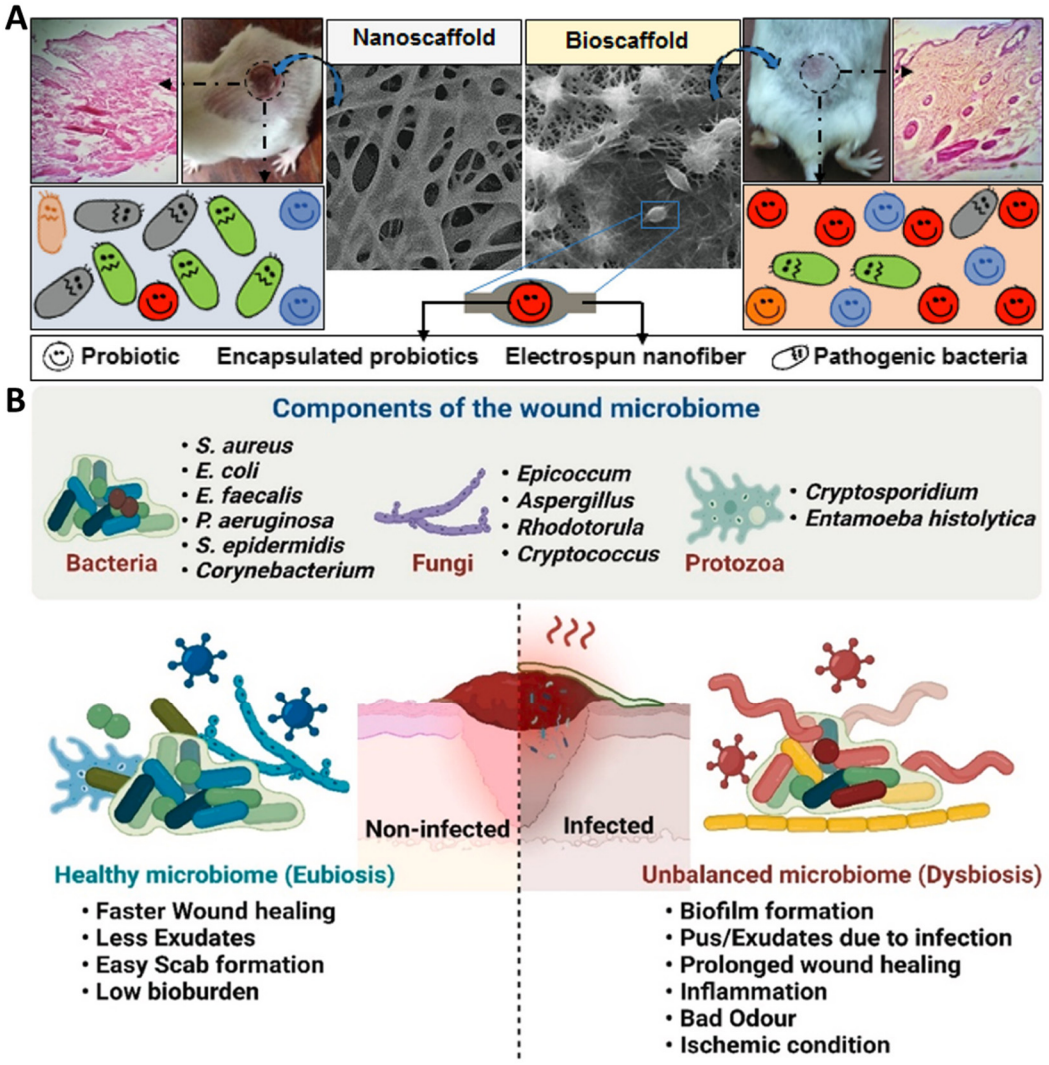

Figure 11. Role of probiotics and probiotic-loaded electrospun scaffolds in modulating the wound microbiome and promoting healing. (**A**) The wound microbiome comprises bacteria, fungi, and protozoa. A healthy microbiome (eubiosis) is associated with faster healing, lower bioburden, and minimal exudate, whereas an unbalanced microbiome (dysbiosis) leads to infection, biofilm formation, prolonged healing, and inflammation. Reproduced with permission from Ref. [223]. Copyright 2019, American Chemical Society. (**B**) Comparative illustration of nanoscale and bio-scale probiotic-loaded electrospun scaffolds demonstrates. enhanced modulation of the wound microbiota, with probiotic encapsulation promoting beneficial bacterial colonization and suppressing pathogenic strains. Histological and in vivo wound images show that these scaffolds support re-epithelialization and reduce inflammation, establishing a favourable microenvironment for tissue regeneration. Reproduced with permission from Ref. [227]. Copyright 2025, Elsevier.

11. Clinical Translation and Real-World Applications of Electrospun Nanofiber Dressings

Spincare™ electrospun nanofiber therapy offers a clinically validated, non-invasive solution that accelerates epithelialization, reduces pain, and improves patient satisfaction in chronic wound care. Its biomimetic nanofiber structure replicates the extracellular matrix, promoting cellular adhesion, migration, and regeneration. The in-situ application enables personalized, conformal coverage while minimizing dressing changes and healthcare resource use. Proper patient compliance with hygiene protocols is critical to maximize therapeutic outcomes and minimize complications [230]. These findings support Spincare™ as an effective, next-generation platform for the real-world management of chronic, non-healing wounds. Beyond preclinical validation, the real-world applicability of

electrospun nanofiber dressings has been supported by several clinical trials. For instance, Haik et al. conducted a multicenter, prospective, randomized study evaluating a portable electrospun nanofibrous matrix for donor site wounds following split-thickness skin grafts [231]. The nanofiber-based dressing demonstrated comparable efficacy and safety to conventional dressings such as Jelonet® and Biatain® Ibu, with lower dermal irritation scores observed on the first postoperative day and similar times to re-epithelialization (17.9 ± 4.4 vs. 18.3 ± 4.5 days). No significant differences were reported in adverse events, pain, infection, itching, or scarring over a 12-month follow-up, underscoring the safety and therapeutic parity of nanofibrous matrices in acute dermal wound management. Additionally, Bagheri et al. demonstrated the effectiveness of amphotericin B-loaded polyvinyl alcohol (PVA) nanofibrous dressings in a clinical pilot study for cutaneous leishmaniasis. The multilayered dressing, fabricated via conventional and needleless electrospinning, enabled controlled drug release and promoted significant healing of non-healing ulcers within four weeks. Its painless application, efficient moisture transfer, and barrier function against infection highlight the broader clinical utility of electrospun nanofiber platforms for infectious and chronic wound care [232]. Moreover, Kossovich et al. developed chitosan-based electrospun nanofiber mats and evaluated them in burn models of IIIa and IIIb severity. The chitosan dressings provided excellent exudate absorption, ventilation, antimicrobial protection, and supported skin regeneration, while their controlled degradation minimized tissue disruption during dressing removal. This early translational evidence reinforces the versatility of electrospun nanofiber technology for diverse clinical wound settings ranging from burns to infected lesions and surgical donor sites [233].

12. Challenges, Limitations, and Future Prospects

Although electrospun nanofiber membranes offer a multifunctional platform for chronic wound management, several translational barriers persist [79]. Key among these is the inconsistency in fiber morphology and drug loading efficiency, often arising from sensitivity to electrospinning parameters and environmental fluctuations. The limited mechanical strength of nanofibers in moist or load-bearing wound sites restricts their application without auxiliary support structures. Moreover, current drug release mechanisms lack the precision to match dynamic wound microenvironmental cues, leading to suboptimal therapeutic efficacy [125,157]. The encapsulation of hydrophilic and large biomolecules remains technically challenging, particularly without compromising structural integrity. Regulatory approval is hindered by the complexity of bioactive composites and insufficient long-term toxicity data. Additionally, manufacturing scalability is constrained by low production throughput and quality control issues across large batches [181,205].

Biological challenges include incomplete understanding of the host immune response to long-term nanofiber implantation, degradation products, and their interactions with wound microbiota. The integration of therapeutic agents often leads to stability issues, especially for proteins and probiotics. Moreover, standardization of in vivo wound models and clinical protocols is lacking, which complicates comparative evaluations [60,174].

Future developments should focus on smart, stimuli-responsive nanofibers capable of modulating drug release in response to pH, temperature, enzymatic activity, or ROS levels. Combining electrospinning with additive manufacturing, microfluidic patterning, or photopolymerization can enable hierarchical structuring and multifunctionality. AI-guided design and real-time biosensing integration may further optimize therapeutic delivery. Addressing these challenges will be crucial to unlock the full translational potential of electrospun nanofiber platforms in personalized wound care [114,205,234].

13. Conclusions

Chronic wound healing remains a formidable clinical challenge, often characterized by a dysregulated microenvironment involving oxidative imbalance, microbial colonization, impaired neovascularization, and immune dysfunction. Electrospun nanofiber scaffolds, owing to their structural similarity to native extracellular matrix and capacity for multifunctional therapeutic delivery, have shown transformative potential in addressing these complex pathologies. Their high surface area, interconnected porosity, and tunable drug-release kinetics enable targeted modulation of cellular and molecular healing pathways.

Despite substantial preclinical progress, the transition of electrospun membranes from bench to bedside is still constrained by several translational bottlenecks. These include batch-to-batch variability, difficulties in encapsulating sensitive biomolecules, and the absence of unified regulatory standards for composite nanostructures. Additionally, reproducibility across scalable manufacturing platforms and the long-term biosafety of embedded agents remain underexplored in clinical contexts.

Emerging strategies such as 3D bioprinting-assisted nanofiber assembly, stimuli-responsive fiber engineering, and integration with biosensing and AI-guided therapeutic feedback loops are redefining the future

of wound therapeutics. These smart platforms have the potential to autonomously adjust drug release in response to wound-state cues such as pH, temperature, ROS, or enzymatic levels—enabling precision medicine at the wound interface. Future research should prioritize the creation of modular, patient-specific nanofiber systems validated through robust in vivo studies and longitudinal clinical trials.

Ultimately, by bridging material innovation with biomedical need, electrospun nanofibers are positioned to evolve beyond passive dressings into intelligent, bioactive systems—capable of orchestrating tissue repair through real-time responsiveness and multifunctional therapeutic synergy.

Author Contributions

Z.R. and Y.X.F. contributed to conceptualization, original draft writing, review, and editing; Y.Y.C., T.L., and V.C. assisted with data curation and visualization; N.N. contributed to reviewing and editing; V.K.T. provided funding acquisition, supervision, and project administration. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new experimental data were generated in this study. Instead, the work is based on comprehensive analysis, synthesis, or reinterpretation of existing information.

Conflicts of Interest

The authors declare no conflict of interest.

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