

REVIEW

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Cite this: DOI: 10.1039/d5tb02803e

Electrospun nanofibers and electrical stimulation: a synergistic approach for chronic wound management

Jéssica Lopes,^{ib abd} Maria Teresa Cruz,^{ib ac} Fernando Ramos^{ib ad} and
Juliana R. Dias^{ib *be}

Electrical stimulation (ES) has emerged as a promising therapeutic approach for enhancing chronic wound healing, addressing the limitations of conventional treatments such as high costs, prolonged recovery times, and suboptimal outcomes. However, traditional ES methods face challenges in delivering uniform stimulation across the wound area. Recent advances in electrospun-based wound dressings, particularly those combined with conductive polymers, offer a solution to these limitations. Conductive electrospun-based wound dressings mimic the skin's extracellular matrix, providing high porosity, a large surface area, and the capacity to deliver ES directly to the wound site, significantly enhancing therapeutic efficacy. This review provides a concise summary of the skin structure, the wound healing process and the effects of ES at various stages of healing. It also explores advanced electrospun-based wound dressings, focusing on the synergistic potential of combining ES with conductive electrospun dressings to optimize chronic wound healing outcomes.

Received 15th December 2025,
Accepted 26th February 2026

DOI: 10.1039/d5tb02803e

rsc.li/materials-b

1. Introduction

Chronic wounds are a growing global concern, contributing significantly to morbidity, amputation risk, and healthcare costs due to limited therapeutic options and to the substantial burden placed on healthcare systems.^{1,2} Notably, 1–2% of the population in developed countries suffers from chronic wounds.³ Based on the etiology, chronic wounds are mainly classified into diabetic ulcers, pressure ulcers and vascular ulcers (venous and arterial ulcers).^{2,4} Despite their diverse origins, chronic wounds exhibit common pathological features, including prolonged inflammation, persistent infections with drug-resistant microbial biofilms, and the accumulation of senescent cells, all of which impede the healing process.^{5,6}

Current wound management strategies include compression therapy,⁷ ultrasound,⁸ negative pressure wound therapy,⁹ debridement,¹⁰ wound dressings,¹¹ and skin substitutes,⁴ but often present challenges such as high costs, prolonged treatment times, and suboptimal healing outcomes.¹² In response

to the limitations of the current approaches, ES emerged as a promising therapeutic strategy for wound healing. Applied as an adjuvant therapy, ES uses current pulses of electromagnetic energy to modulate cellular activity and accelerate wound healing.^{6,13} *In vitro* studies have demonstrated that ES enhances wound healing at all stages by increasing blood flow, exhibiting antibacterial effects, and inducing key cell responses involved in the healing process.^{14–16} Similarly, *in vivo* and clinical investigations have shown beneficial effects of ES in treating chronic wounds,^{17–20} supporting its therapeutic potential. Although ES has shown significant promise as an independent therapy for wound healing, traditional electrode-based strategies, which involve placing electrodes directly on the skin or the wound site, are limited by their inability to provide uniform stimulation across the entire wound area.²¹ Several studies have demonstrated that applying ES through a conductive wound dressing that fully covers the wound is more effective than using electrodes alone in promoting chronic wound healing.^{21–26} The effectiveness of this strategy is due to the distinctive attributes of electrospun meshes, including high porosity, high surface area-to-volume ratio, and their resemblance to the extracellular matrix (ECM).²⁷ When combined with conductive polymers, these electrospun-based wound dressings enable the direct delivery of ES to the wound site, enhancing its therapeutic efficacy.^{28,29} This innovative strategy, combining ES with conductive electrospun-based wound dressings, has demonstrated superior outcomes in

^a University of Coimbra, Faculty of Pharmacy, Portugal^b Centre for Rapid and Sustainable Product Development (CDRSP), Polytechnic Institute of Leiria, Marinha Grande, 2030-028, Portugal^c Center for Neuroscience and Cell Biology, University of Coimbra, Portugal^d REQUIMTE/LAVQ, University of Coimbra, Coimbra, Portugal^e SPMET - Sociedade Portuguesa de Medicina Regenerativa, Engenharia de Tecidos e Terapia Celular, Leiria, Portugal

accelerating the wound healing process and skin tissue regeneration in chronic wounds.^{24,25,30}

This review offers a concise overview of skin structure and the wound healing process, assesses the role of electrospun fibers and their impact on various stages of healing, and explores advanced electrospun-based wound dressings, both non-conductive and conductive, highlighting the integration of conductive polymers. Distinctively, it highlights the synergy between ES parameters and the properties of conductive electrospun nanofibers, addressing translational barriers and clinical applicability in chronic wound care.

2. Skin, wound healing and influence of innate conductivity

2.1. Skin structure

Healthy skin acts as a barrier between the human body and the external environment. It maintains homeostasis by regulating body fluids and electrolyte balance, preventing water loss, and controlling body temperature.³¹ Furthermore, the skin plays crucial roles in sensorial perception, vitamin D synthesis, and immune response.^{32–34} The skin comprises three distinct layers: the epidermis, dermis, and hypodermis (Fig. 1). The epidermis, the outermost layer of the skin, is mainly constituted by keratinocytes, but also melanocytes, Merkel cells, and Langerhans cells.³³ It forms a crucial barrier, preventing the entry of pathogens and minimizing water and electrolyte loss.³⁵ The following layer is the dermis, a connective tissue characterized by its ECM. The ECM is made of interconnected structural proteins (collagen, elastin, fibronectin and laminin), proteoglycans (heparan sulfate, chondroitin sulfate, and keratan sulfate) and glycosaminoglycans (hyaluronic acid), which provide strength, flexibility and support to the skin.³³ Dermis is also rich in blood vessels, nerves, and diverse cell types, including fibroblasts, mast cells, macrophages and endothelial cells, important in the healing process.³⁶ Then, hypodermis, the

deepest layer, is primarily composed of adipose tissue, which helps body temperature regulation and provides structural support.³⁷ The coordinated function of the different layers, each with distinct cellular composition and functions, is essential for successful wound healing and the restoration of the skin's protective barrier.

2.2. Stages of wound healing and tissue repair

The skin has developed rapid and efficient mechanisms to respond to injuries, which induce a cascade of events to re-establish the skin's structure and function in case of cutaneous barrier disruptions.³⁸ The process involves the activity of various cells, including keratinocytes, fibroblasts, endothelial cells, macrophages, neutrophils, monocytes, and lymphocytes.³⁹ Additionally, it relies on extracellular components and soluble mediators, such as growth factors and cytokines, to regulate tissue repair.⁴⁰ Although the process is dynamic and with overlapping stages, the wound healing process typically consists of five different phases: hemostasis, inflammation, migration, proliferation and maturation (remodeling)^{41,42} (Fig. 2).

The hemostasis phase begins immediately after the injury, with vasoconstriction and platelet aggregation to prevent further bleeding and the entry of pathogens.⁴³ This process initiates the coagulation cascade, where prothrombin converts fibrinogen into fibrin, forming a fibrous mesh that stabilizes the clot and seals the wound.⁴⁴ Simultaneously, delivers essential growth factors and cytokines, such as epidermal growth factor (EGF), transforming growth factor (TGF)- α and TGF- β , insulin growth factor (IGF), interleukin-1 (IL-1), and platelet derived growth factor (PDGF), to the inflammatory site, thereby initiating wound healing through the activation of neutrophils, lymphocytes, macrophages, and mast cells.^{45,46}

During the inflammatory phase, neutrophils are the first to arrive, followed by macrophages, which work to eliminate bacteria and clear tissue debris, thereby preventing potential infection.^{41,47} Macrophages, in addition to participating in phagocytosis, release more cytokines and growth factors that

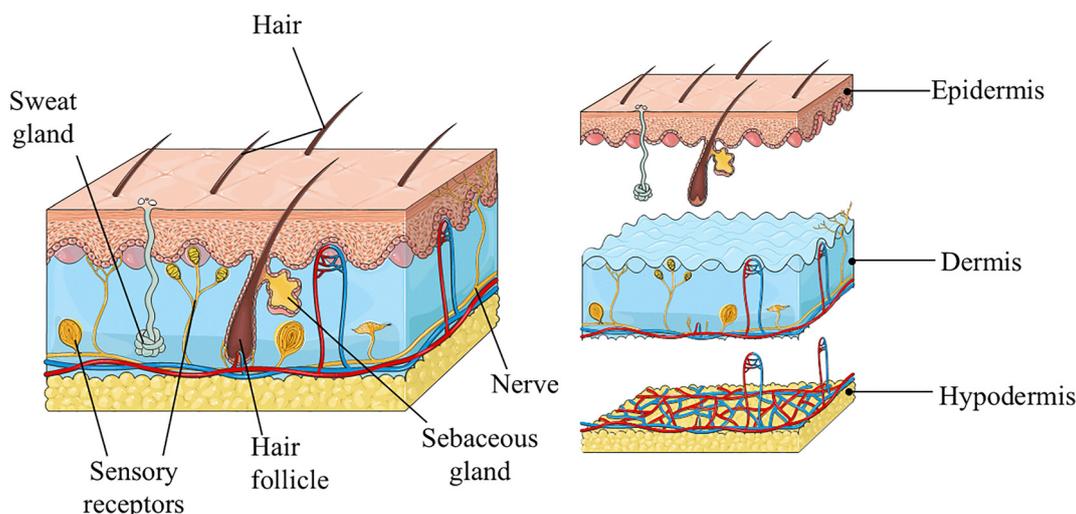


Fig. 1 Skin structure. This figure was obtained and modified from Servier Medical Art (<https://smart.servier.com/>).



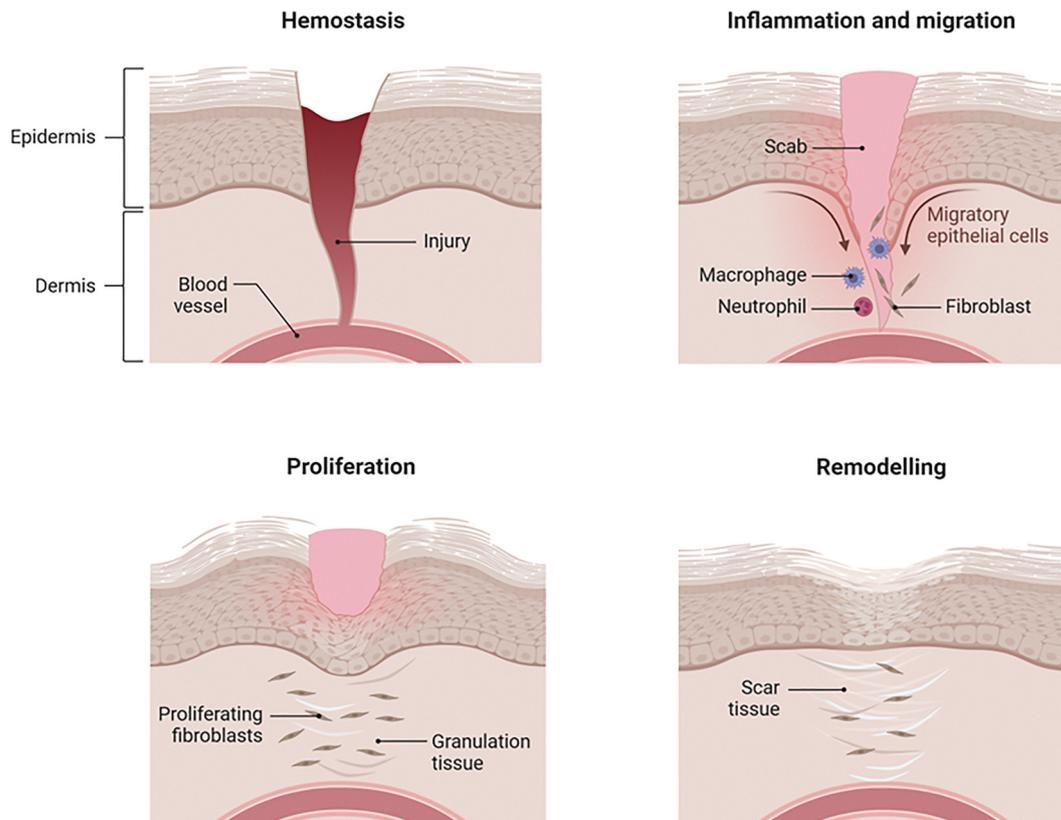


Fig. 2 Wound healing phases: hemostasis, inflammation, migration, proliferation and remodeling. Adapted from an image created with <https://BioRender.com>.

promote fibroblast proliferation, angiogenesis, and keratinocyte migration.⁴⁸ Some researchers consider migration and proliferation as a single phase because they are highly interrelated.^{38,45,49} Epithelial cell migration replaces dead cells, resulting in the reduction of inflammation.⁵⁰ In the proliferation phase, the injury is covered with epithelial cells and macrophages, while fibroblasts and endothelial cells migrate to the damaged area to create a granular tissue containing a new matrix and blood vessels, respectively.^{38,45} During this phase, fibroblasts play a central role by depositing immature type III collagen on a temporary matrix for the migration and proliferation of other cells involved in the healing process.^{48,51} Furthermore, the release of TGF- β by platelets and macrophages enhances the production of matrix components, as collagen, proteoglycans and fibronectin.⁵² The formation of new blood vessels – angiogenesis – begins during the early hemostatic phase with thrombus formation and becomes more pronounced in the proliferative phase.⁵³

After the wound is fully re-epithelialized, the healing process evolves to tissue remodeling and reconstruction.⁵⁴ The final stage, maturation, involves the process of tissue remodeling during which fibroblasts can differentiate into myofibroblasts, producing abundant ECM proteins, and contributing to the formation of a new skin layer over the injured area.^{55,56} During this phase, the rapidly synthesized type III collagen in the ECM is replaced by the type I, which provides greater tensile strength but requires more time to accumulate.^{57,58} Therefore, the

maintenance of tissue integrity after injury is achieved through the development of a scar.⁵⁹ Myofibroblasts form scars by increasing collagen-rich ECM production and structuring this matrix with high contractile forces.⁵⁶ In healthy wound healing, myofibroblasts undergo apoptosis once the wound is closed, preventing excessive scar formation.⁶⁰

2.3. Pathophysiology and progression of chronic wounds

Chronic wounds, according to their definition, do not follow this series of events. They are characterized by a dysfunctional healing process, where the critical phases of proliferation and remodeling are hindered, which prevents the wound from progressing beyond the inflammatory state, resulting in delayed or incomplete healing.⁶¹ Chronic wounds present typically persistent inflammation, driven by the excessive production of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-alpha (TNF- α).⁶² These cytokines stimulate excessive production of reactive oxygen species (ROS), which can cause oxidative stress and induce cellular damage in fibroblasts and keratinocytes.⁶³ This inflammatory environment stimulates protease activity, leading to the degradation of the ECM, disruption of growth factor signaling pathways, and ultimately, impaired angiogenesis.⁴ The resulting insufficient angiogenesis restricts nutrient delivery and metabolic waste removal, thereby further delaying tissue repair and wound healing.⁶⁴



Moreover, in chronic wounds, neutrophil function is significantly impaired, characterized by altered phenotypes, reduced infiltration, and persistence within the wound bed.^{6,65} Simultaneously, macrophages exhibit predominantly a M1 phenotype, with excessive production of pro-inflammatory cytokines, contributing to a persistent inflammatory environment.⁶⁶

Wounds also provide a favorable environment for microorganisms from the skin microbiota and the external environment to enter and colonize deeper tissues.⁶⁷ In chronic wounds, the presence of necrotic tissue and cellular debris promotes biofilm formation, facilitating bacterial attachment, while compromised host immune defenses further increase susceptibility to infection.^{68,69} Although chronic wounds arise from different etiologies and can be colonized by multiple microbial species, *Staphylococcus* and *Pseudomonas*, are the most frequently identified genera associated with biofilm formation.⁷⁰ Together, these factors challenge the effective treatment of chronic wounds, highlighting the need for alternative therapeutic strategies.

3. Endogenous fields and exogenous stimulation in wound healing

3.1. Endogenous electric field in skin wounds

Healthy human skin possesses a transepithelial potential (TEP) ranging from 10 to 60 mV, varying across different body

locations. This potential arises from the movement of ions *via* Na^+/K^+ ATPase (sodium/potassium pump) in the epidermis.^{29,71} The asymmetric distribution of ion channels within epithelial cells, with Na^+ and Cl^- channels predominantly located on the apical plasma membrane and K^+ channels and Na^+/K^+ -ATPase pumps localized in the basal plasma membrane, creates an electrochemical gradient that drives the flow of ions, resulting in the generation of the observed electrical current across the cell^{72,73} (Fig. 3A).

When a skin wound occurs, the disruption of the epithelial barrier leads to the generation of an endogenous electric field within the wound, reaching 100 to 200 mV mm^{-1} .⁷¹ The injured epidermis, which has a TEP, becomes electrically negative relative to the intact, positively charged surrounding skin, creating a current flow into the wound center^{73,74} (Fig. 3B).

The intensity of this field gradually decreases as the wound heals, and TEP is reestablished.⁷¹ Compared with acute wounds, chronic wounds exhibit a weaker endogenous electric field, potentially contributing to delayed healing.⁷⁵ The electrical fields produced by these injured tissues have been proposed to play a significant role in cell migration and orientation, protein synthesis, distribution, and activation.^{71,76,77} Furthermore, it was found that the current produced by skin disruption creates a gradient that activates cell migration, including keratinocytes, towards the wound bed to initiate proper healing, a phenomenon known as galvanotaxis.^{14,76,78} These endogenous electric fields

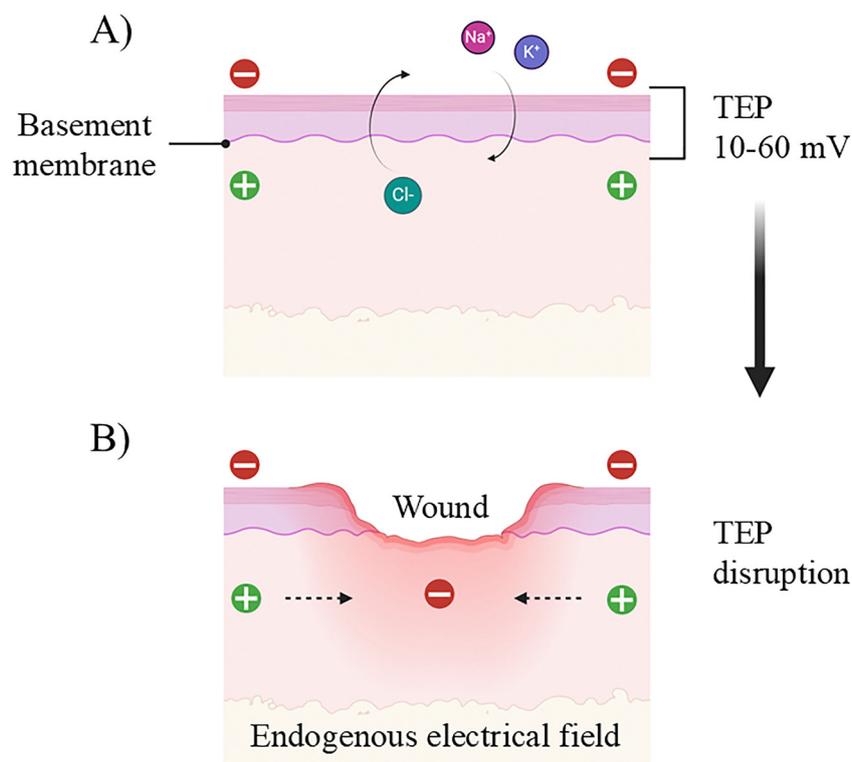


Fig. 3 Representation of transepithelial potential (TEP) generation on intact skin and endogenous electric fields in skin wounds. (A) In intact skin, TEP ranges from 10 to 60 mV, generated by the ionic flow of Na^+ , K^+ , and Cl^- . (B) In the case of a wound, the TEP is disrupted, resulting in the generation of an endogenous electrical field, where the wound site becomes electrically negative relative to the surrounding intact tissue, positively charged. This image was created with <https://BioRender.com>.



encouraged the potential use of exogenous ES to accelerate wound healing.

3.2. ES and their applications in skin wound healing

Exogenous ES is broadly defined as the application of electrical current through electrodes placed on the skin, near or directly on the wound, to replicate the endogenous electric current.^{29,79} Various modes of ES, including direct current (DC), pulsed current (PC), alternating current (AC), and their subtypes, have been described in the literature,^{73,77,80,81} and are represented in Fig. 4.

DC is characterized by a unidirectional flow of charged particles, resulting in constant polarity, which mimics the endogenous electric field.⁷³ Studies on DC have shown that it accelerates the inflammatory phase, allowing a faster transition to the proliferative phase, and has also demonstrated beneficial effects on the remodeling phase.⁸² Additionally, DC was tested on pressure ulcers, where it effectively accelerated wound area reduction and resulted in the complete healing of some ulcers.⁸³ However, prolonged DC application may cause tissue irritation due to pH changes in the skin.⁷⁷

On the other hand, PC is a unidirectional or bidirectional current flow and can have two waveforms: monophasic or biphasic.⁸⁰ Monophasic PC, which can be further classified as low-voltage (LVPC)⁴⁰ or high-voltage (HVPC),⁸⁴ flows in only one direction and is one of the most studied waveforms for wound therapy, as discussed below. Both PC and DC are delivered to wound tissues through conductive coupling, which involves filling the wound defect with a hydrogel or moist gauze that acts as a conductive medium, and then placing electrodes on the surface.⁸⁰ An advantage of PC is that it shows fewer

electrical thermal, physical, and chemical side effects than DC.^{81,85}

Randomized trials have evaluated HVPC for the treatment of venous leg ulcers,⁸⁶ pressure ulcers,^{87,88} or diabetic foot ulcers,⁸⁹ consistently reporting its effectiveness in promoting wound healing.^{86–90} Another clinical trial tested different durations of HVPC stimulation on patients with ulcers and showed that 60 minutes of stimulation seven days a week can significantly reduce the wound surface area.⁸⁷ Likewise, a study compared different ES on chronic wounds, including DC, LVPC and HVPC, and concluded that HVPC showed the best improvement in chronic wound size reduction.¹⁸ Instead, LVPC application has demonstrated antimicrobial effects, reducing common Gram-positive and Gram-negative pathogens associated with chronic wounds.⁹¹

Alternatively, AC is a continuous bidirectional flow current that changes its direction and magnitude periodically.⁸¹ In a pig wound, both AC and DC demonstrated a reduction in healing time. However, DC appeared more effective in decreasing wound area, while AC showed a greater efficiency in reducing wound volume.⁹² Transcutaneous electrical nerve stimulation (TENS) is a type of AC, where the electrodes are placed on intact skin adjacent to the wound.⁹³ Physicians often use TENS for pain management by activating peripheral nerves, in both chronic and acute cases.⁹⁴ Studies in animal wound models have shown that TENS can improve angiogenesis and also reduce pro-inflammatory cytokines in the skin, suggesting that it may contribute to the healing process by inhibiting the inflammatory phase.^{95,96} FREMS (frequency rhythmic electrical modulation systems) is also a form of transcutaneous electrotherapy that uses automatically modulated electrical pulses, varying in frequency, duration, and voltage.¹² Several

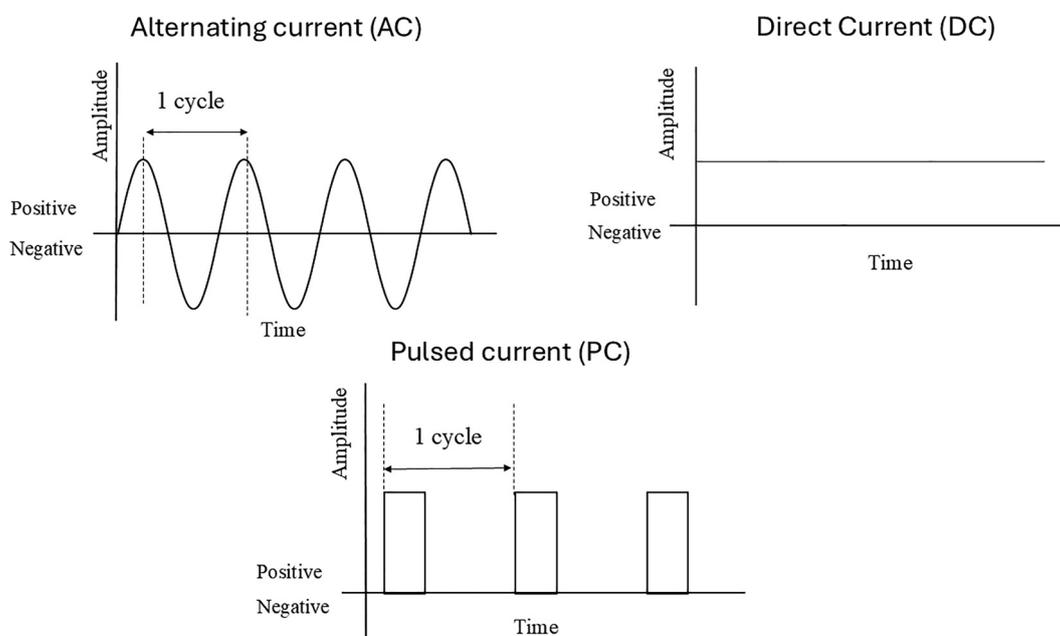


Fig. 4 Representation of different electrical waveforms delivered for wound healing, including alternating current (AC), direct current (DC) and pulsed current (PC).



Table 1 Summary of studies on skin wound healing induced by ES based on waveform type

Type of ES	Treatment characteristics	Tested on	Key outcomes	Ref.
DC	Intensity (<i>I</i>): 300 μA , 30 min day^{-1} , starting with negative polarity and then changed after 3 days 3 sessions per day of 20 min, and then reduced to 2 daily after 14 days	Incision wound (rats)	Faster wound healing process	82
		Pressure ulcers	Reduced wound area and healing time	83
HVPC	150 V; interphase interval of 100 μs ; frequency (<i>F</i>): 100 Hz; 3 times per week, for 4 weeks 100–175 V, interphase interval of 50 μs ; <i>F</i> : 120 Hz, during 45, 60, or 120 min; 7 days 100 V; interphase interval of 100 μs ; <i>F</i> : 100 Hz; 50 min day^{-1} , 5 times per week 50 V; interphase interval of 100 μs ; 160 min day^{-1} , 7 days week^{-1}	Mixed ulcers	Reduced wound surface area	86
		Chronic pressure ulcers	Reduced wound surface area	87
		Pressure ulcers	Reduced wound area and increased the granulation tissue	88
		Diabetic foot ulcers	Increased wound closure	89
LVPC	<i>I</i> : 42 mA; <i>F</i> : 28 Hz; 30 min	Cotton patch (simulation of a wound)	Antibacterial effect	91
AC or DC	AC (4 s on and 4 s off), amplitude: 7–10 mA; interphase interval of 300 ms; <i>F</i> : 40 Hz. DC: constant amplitude: 0.6 mA; 2 h day^{-1} , 5 days week^{-1} , for up to 30 days	Incision wound (pig)	Reduced healing time; AC reduced the wound volume more rapidly, while DC reduced wound area more rapidly	92
TENS	<i>I</i> : 15 mA; interphase interval of 200 μs ; high-frequency (80 Hz) or low-frequency (5 Hz); for 60 min, for 3 consecutive days <i>F</i> : 2 Hz; interphase interval of 250 μs ; 15 min, for 5 days	Excision wound (rats)	Improved angiogenesis	96
		Incision wounds (rats)	Reduced pro-inflammatory cytokines	95
FREMS	12 sessions in 4 weeks (3 sessions per week), until full wound healing, or for a maximum of 9 ES cycles, with a 2-week rest between cycles 3 consecutive weeks/15 treatment sessions 3 consecutive weeks/15 treatment sessions (5 days week^{-1}), for 40 min	Chronic leg ulcers	Improved healing and pain reduction	13
		Venous leg ulcers	Reduced wound area and pain reduction	98
		Chronic leg ulcers	Accelerated wound healing and reduced pain	97

ES- electrical stimulation; DC- direct current; HVPC- high-voltage pulsed current; LVPC- low-voltage pulsed current; AC- alternating current; TENS- transcutaneous electrical nerve stimulation; FREMS- frequency rhythmic electrical modulation systems.

randomized controlled trials have demonstrated that FREMS, as an adjuvant therapy, helps with pain relief and effectively reduces wound area in patients with chronic ulcers.^{13,97,98} Table 1 provides a summary of *in vitro* and *in vivo* studies on various types of ES applied to wounds, along with their respective outcomes.

Overall, numerous preclinical and clinical studies have demonstrated that electrospun fibers offer beneficial effects at various stages of wound healing, highlighting their potential for clinical application.^{20,99–108} During the inflammatory phase, there is an increase in vasodilatation, which recruits more immune cells, including leukocytes, platelets, and macrophages.¹⁰¹ ES improves macrophage migration, thereby reducing edema and inhibiting bacterial growth.^{12,109} According to Hoare *et al.*, (2016), the movement of macrophage migration is directly proportional to the strength of the field, resulting in increased phagocytosis.¹¹⁰ The exposure to an electric field can activate the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and Phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathways. The MAPK-ERK cascade serves as a key mediator of extracellular signals within various signaling networks, with MEK phosphorylation driving cell migration through the activation of downstream kinases ERK1 and ERK2.⁴⁰ Activation of the MAPK-ERK1 pathway also elevates intracellular Ca^{2+} levels, including transient receptor potential Vanilloid 2 (TRPV2)-dependent Ca^{2+} influx in macrophages, thereby improving their bacterial phagocytic capacity.^{111–113}

Chronic wounds are frequently colonized with bacteria, leading to chronic inflammation and delayed healing due to the excessive release of bacterial toxins and inflammatory signals.^{114,115} AC stimulation has been shown to inhibit the growth of the Gram-positive bacteria *Staphylococcus epidermidis*, however, DC appears to have a stronger inhibitory effect on bacteria than AC.¹¹⁶ Another research on *Escherichia coli* revealed that DC caused leakage through the membrane, resulting in the release of proteins, and causing the death of bacteria.¹¹⁷ The bacteriostatic and bactericidal effects of ES may reduce bacterial load in the wound bed, thereby creating a more favorable environment for wound healing.¹¹⁸

Simultaneously, ES accelerates the transition of the wound to the proliferative phase, an essential step in avoiding chronic wounds.¹¹⁹ These occurrences improve inflammatory responses, resulting in higher oxygen levels in the tissues, improved blood flow, and elevated skin temperature.¹⁰⁹ The proliferative phase of wound healing includes angiogenesis, fibroplasia, and re-epithelialization¹²⁰ and involves two key cell types: fibroblasts in connective tissue and keratinocytes responsible for wound re-epithelialization.¹²¹

ES promotes keratinocyte proliferation and differentiation, leading to increased keratin production and faster migration, essential to restoring an intact epidermis,^{105,106} while reducing the pro-inflammatory cytokines (IL-6 and IL-8).¹²¹ A research study showed that ES exposure at physiological magnitudes (50–200 mV mm^{-1}) increased human keratinocyte viability and



proliferation.¹²¹ Fibroblasts are necessary for the wound healing process at different phases, as they produce a large number of proteins, including fibronectin, elastin, collagen I and II, and other proteins that form the ECM required for the development of new tissue.^{107,122,123} Studies have shown that fibroblasts exhibit increased collagen deposition and accelerated migration in response to ES.^{105,106}

Additionally, ES can significantly enhance the secretion of fibroblast growth factor 1 (FGF-1) and fibroblast growth factor 2 (FGF-2), leading to a rebalancing of cell migration, proliferation, and differentiation.⁵⁵ Fibrogenesis plays a key role in granulation tissue formation, requiring fibroblast migration to ensure proper wound coverage.¹⁰⁶ The upregulation of angiogenic factors such as FGF-1, FGF-2, and vascular endothelial growth factor (VEGF) highlights the therapeutic potential of ES, which can enhance wound healing by stimulating angiogenesis and promoting endothelial cell migration and proliferation to restore vascularization.^{106,112}

Finally, ES improves the remodeling stage by increasing myofibroblast contractility and converting collagen from type III to type I, reorganizing collagen fibers to strengthen scars.^{55,106} This highlights the crucial role of ES not only in accelerating wound closure but also in enhancing the structural quality and strength of the repaired tissue. While ES shows promise for the treatment of chronic wounds, electrode-based approaches may have limited efficacy due to uneven current distribution across the wound bed.²¹ The use of wound dressings to deliver ES directly to the injured tissue could potentially overcome this limitation.

Despite substantial research into the clinical applications of ES, standardized parameters for its administration remain undefined, reflecting both the heterogeneity of therapeutic objectives, ranging from pain relief to muscle contraction and rehabilitation, and the need to tailor therapy to the individual patient. Variations in parameters such as current intensity, pulse duration, electrode type, and placement can differentially influence key biological processes, including cell migration, proliferation and differentiation.¹²⁴

Optimal ES aims to minimize adverse effects, closely replicate endogenous physiological electric fields, and maximize cellular responses. In the absence of established protocols, clinicians empirically adjust parameters to optimize outcomes. For example, reducing pulse width while increasing pulse frequency has been shown to attenuate side effects while preserving therapeutic efficacy,¹²⁵ highlighting the importance of tailoring ES to both patient characteristics and specific therapeutic goals.

3.2.1. Clinical applications of electroceutical dressings. Several commercially available dressings and devices exemplify the clinical application of ES in wound care. Procera[®] (Vomaris Inc., USA) is an antibacterial wound dressing composed of microcell batteries created by alternating deposits of zinc and silver on a polyester substrate, primarily designed for the treatment of partial and full-thickness wounds.¹²⁶ When activated by a conductive medium such as wound exudate or water-based wound hydrogels, it generates galvanic microcurrents in the microampere range ($\sim 10 \mu\text{A}$).¹²⁷

In a clinical study, Blount *et al.* applied Procera[®] bandage to 50% of the donor sites in 13 patients undergoing skin grafting and reported improved wound healing, scarring, and favorable subjective patient outcomes.¹²⁸ Furthermore, two additional studies demonstrated that Procera[®]-treated wounds generally healed faster, required fewer dressing changes, and reduced overall treatment costs.^{129,130} At a molecular level, it improved keratinocyte migration, which is of relevance in wound re-epithelialization.¹³¹ Nevertheless, silver is a heavy metal with potential cytotoxic effects, including protein denaturation.¹³² Moreover, the available evidence remains limited, and more extensive studies are needed.

PosiFect[®]RD (Biofisica LLC, Atlanta, GA) is another microcurrent-generating dressing, developed for the treatment of chronic ulcers, including venous and pressure ulcers.^{133,134} The dressing consists of a metal ring (anode) placed outside the wound and a small paddle (cathode) placed at the center of the wound bed to direct current in the wound bed.⁷⁴ The microcurrent is generated by two non-rechargeable batteries and a miniature control circuit to maintain a stable DC for at least 48 hours.¹³⁵ A clinical study suggests that PosiFect RD[®] promoted total wound closure in less than 3 months.¹³³

Accel-Heal[®] represents a different approach: functioning as a disposable, compact system that delivers continuous low-voltage pulsed current (both biphasic and monophasic) through an integrated electronic module, enabling standardized ES therapy for up to 48 hours without the need for external devices or additional handling.¹³⁶ However, during a typical 12-day treatment course, the electrodes must be replaced every 48 h to maintain effective stimulation.⁷⁴ A clinical study with Accel-Heal[®] reported accelerated healing progression and significant pain reduction in patients with hard-to-heal wounds.¹³⁶

WoundEL[®], is also a battery-powered electrostimulation system in which electrodes are integrated directly into the dressing and connected to a portable generator that delivers LVPC, allowing controlled and localized ES application.⁸⁰ The dressing itself is composed of a hydrogel contact layer interfacing with the wound, a conductive carbon-silver middle layer, and an outer water-repellent protective layer.^{137,138} Therapy sessions are typically performed once daily for 20–30 minutes over a period of 2–3 days.¹³⁷

These devices illustrate the practical implementation of ES in wound care, providing active, ready-to-use solutions that can modulate cellular behavior, reduce infection, and accelerate healing. However, despite promise, currently available electroceutical dressings and devices present important limitations. Their stimulation parameters are usually pre-set, offering limited flexibility for patient-specific customization. Moreover, the electroactive elements, such as metallic electrodes or silver-zinc systems, raise concerns regarding long-term biocompatibility and local cytotoxicity. Also, the lack of large-scale randomized clinical trials confirming long-term safety and efficacy further hampers their widespread clinical translation. These limitations underscore the need for next-generation wound dressings.



4. Advanced electrospun-based wound dressings

Traditional wound dressings, such as gauze, lint, and bandages, may be cost-effective but often fail to adequately address the complexities of chronic wound healing, leading to prolonged healing times.¹³⁹ Besides, these dressings may adhere to the wound bed, causing potential damage and pain when replaced regularly.¹⁴⁰ Nevertheless, nanofiber meshes fabricated by electrospinning exhibit significant potential for advanced wound dressing applications due to their unique properties. Firstly, their structural and functional similarity to the skin ECM provides an ideal microenvironment for cell adhesion, proliferation and migration.¹⁴¹ Secondly, the high surface area contributes to enhanced hemostasis and efficient absorption of wound exudate.⁴¹ Lastly, their porous structure facilitates gas exchange, allowing oxygen to reach the wound bed while maintaining a moist environment due to their semi-permeability, and acts as a physical barrier preventing bacterial infection.^{28,41}

These remarkable characteristics result from electrospinning, an electrostatic fiber fabrication technique that has garnered significant attention in recent years due to its broad applicability across diverse fields.¹⁴² The conventional electrospinning apparatus is composed of a high-voltage source, a syringe pump, a spinneret and a collector.¹⁴² Briefly, a polymeric solution is loaded into a capillary tube and restrained by its surface tension. When a high voltage (5 to 30 kV) is applied between the needle and the collector, the solution is ejected from the tube.¹⁴³ As the solution jet passes through the air, the solvent evaporates, leading to the deposition of nanofiber meshes onto the collector.⁵⁰

A key advantage of electrospinning is the ability to tailor the structural properties of nanofibers by adjusting several parameters, namely: solution parameters (*e.g.* polymer type, solvent, viscosity, conductivity, surface tension), process parameters

(*e.g.* voltage, flow rate, needle diameter, distance between the needle tip and collector), and ambient parameters (*e.g.* humidity and ambient temperature).^{50,144} Based on these advantageous properties, electrospun meshes are considered a promising option for the development of advanced wound dressings.

4.1. Non-conductive wound dressings

Different types of polymers, including natural and synthetic polymers, have been electrospun into nanofibers for wound dressings.¹⁴⁵ Natural polymers such as chitosan (CS), gelatin (GE), collagen, silk fibroin, and hyaluronic acid (HA), are highly attractive due to their excellent biocompatibility, good biodegradability and affordability.^{146,147} However, they present significant challenges, including weak mechanical properties and variability in properties depending on their source.¹⁴⁸

For instance, Ebrahimi-Hosseinzadeh *et al.*, (2016) prepared nanofibrous membranes with two natural polymers: HA and GE, and they were tested *in vitro* and *in vivo* on a second-degree burn wound. After two weeks, the experimental group treated with the HA/GE scaffold exhibited a significant 17% improvement in wound closure compared to the control group¹⁴⁹ (Table 2). Furthermore, a novel electrospun wound dressing composed of GE and CS, doped with a phlorotannin-rich extract from the seaweed *Undaria pinnatifida*, demonstrated antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This dressing showed the potential to serve as a drug delivery system and significantly reduce bacterial infections within wound beds.¹⁴⁴

Synthetic polymers have also been used for the fabrication of electrospun nanofibers for wound healing applications. They offer superior mechanical properties and a more controlled structure, but their biological properties are inferior to those of natural polymers.^{154–156} There are various synthetic polymers, such as poly(lactic acid) (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA), and

Table 2 Selected examples of non-conductive wound dressings categorized by the polymers type

Polymers	Polymers type	Dressing components	Dressing form	Fabrication method	<i>In vitro/ in vivo</i> studies	Wound type	Highlights	Ref.
GE + HA	Natural–natural	Gelatin/hyaluronic acid	Scaffold	Electrospinning/crosslinking	Yes/yes	Burn wounds	Reduced inflammation and accelerated wound closure	149
GE+ CS	Natural–natural	Gelatin/chitosan/phlorotannin-enriched extract	Nanofibers	Electrospinning	Yes/no	Chronic wounds	Increased fibroblast attachment, proliferation, and antimicrobial activity	144
PCL + PVA	Synthetic–synthetic	PCL/PVA/AgNPs	Nanofibers	Electrospinning	Yes/yes	Full-thickness wounds	Antimicrobial activity and biocompatibility with human fibroblasts	150
PCL+ PEG	Synthetic–synthetic	PCL/PGE/Nisin	Nanofibers	Electrospinning	Yes/no	Infected wounds	Enhanced exudate absorption and antibacterial activity	151
PLGA + Collagen	Synthetic–natural	PLGA/collagen/glycophage	Membranes	Electrospinning	Yes/yes	Diabetic wounds	Faster wound closure, improved re-epithelialization, and increased collagen I content	152
PCL + GE	Synthetic–natural	ϵ -PL/PCL/GE	Scaffold	Electrospinning/crosslinking	Yes/no	Infected wounds	High antimicrobial activity and excellent biocompatibility with human skin cells	153

GE, gelatin; HA, hyaluronic acid; CS, chitosan; PCL, polycaprolactone; PVA, polyvinyl alcohol; AgNPs, silver nanoparticles; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); ϵ -PL, ϵ -polylysine.



polycaprolactone (PCL), that have been approved by the US Food and Drug Administration (FDA) for tissue engineering applications.^{155,157}

Each synthetic polymer has its advantages, and the combination of different polymers can potentially enhance wound healing.¹⁵⁸ As an example, Mina Mohseni and colleagues developed two series of PCL/PVA nanofiber wound dressings loaded with different concentrations of silver sulfadiazine (SSD) or silver nanoparticles (AgNPs) to compare both *in vitro* and *in vivo*. The results showed that both had antimicrobial activity, but SSD presented more cytotoxicity against fibroblast cells. Additionally, dressings loaded with AgNPs demonstrated significantly accelerated wound closure, reduced inflammatory response, and presented high biocompatibility against human fibroblast cells, leading to enhanced angiogenesis, epithelialization, and tissue remodeling.¹⁵⁰ Another application of synthetic polymer nanofibers was proposed by S. Silpa & S. Rupachandra (2024).¹⁵¹ They fabricated a PCL/polyethylene glycol (PEG) nanofiber wound dressing loaded with nisin, an antibiotic from *Lactococcus lactis*. This innovative dressing exhibited excellent exudate absorption and antimicrobial activity against both Gram-positive and Gram-negative bacteria.¹⁵¹

Synthetic polymers have made significant advancements in the field of wound dressings. However, their inherent limitations, such as poor cell attachment, limited biocompatibility and biodegradability, have restrained their broader application.^{158,159} Hence, the combination of synthetic and natural polymers has been used to take advantage of the benefits of both types of polymers. For instance, Lee *et al.*, (2015) fabricated nanofibrous membranes made of collagen and PLGA loaded with metformin.¹⁵² PCL is a biopolymer with tensile properties compared to epithelial tissues, while collagen dressings have been found to reduce bacterial protease activity. Additionally, metformin, an antidiabetic drug, has been found to enhance re-epithelialization in diabetic wounds. This study demonstrated that these collagen/PLGA nanofibers effectively delivered the drug for over 3 weeks, providing a continuous supply for wound repair. *In vitro* testing showed significantly faster wound healing, better re-epithelialization and a higher content of collagen I in diabetic rats. These findings suggest that collagen/PLGA nanofibers loaded with metformin hold significant promise for accelerating skin regeneration by increasing collagen content in the treatment of diabetic wounds.¹⁵²

Another example is the Ghomi *et al.*, (2023) research, where they developed a novel wound dressing with a combination of features to promote wound healing.¹⁵³ They incorporated ϵ -polylysine (ϵ -PL) into electrospun scaffolds made of PCL and GE. The researchers crosslinked the scaffolds using dopamine hydrochloride, which resulted in highly proliferative dressings. Also, fiber alignment of the electrospun PCL/GE scaffolds improved their tensile strength. The incorporation of ϵ -PL provided the dressings with antibacterial activity against various bacteria that are commonly associated with wounds. Moreover, *in vitro* testing with human skin cells showed excellent biocompatibility of the dressings, especially in the aligned

samples. Overall, fiber alignment potentially contributed to improved cell attachment and proliferation, indicating that aligned PCL/GE mats containing ϵ -PL are promising for potential use in wound dressings.¹⁵³ Table 2 summarizes these examples of non-conductive wound dressings.

4.2. Conductive wound dressings

Researchers have been developing conductive dressings with electrical conductivity similar to human skin (ranging from 2.6 to 1×10^{-4} mS cm⁻¹) achieved by the incorporation of conductive polymers (CPs).^{22,160–164} CPs represent a class of organic materials exhibiting electrical and optical properties similar to inorganic semiconductors and metals.¹⁶⁵ Due to their biocompatibility and inherent antioxidative and antibacterial properties, CPs have extensive applications in biomedicine, particularly wound healing dressings.^{28,166–168}

Among them, polypyrrole (PPy), polyaniline (PANI), and poly(3,4-ethylenedioxythiophene) (PEDOT) are the most widely studied for skin tissue applications due to their excellent electro-optical properties, good biocompatibility, and versatile doping chemistry.²⁸ In addition to serving as a conductive substrate, CPs significantly influence the fundamental material properties of wound dressings. Although *in vitro* studies report favorable cytocompatibility profiles, the overall safety of CP-based systems remains under active investigation, particularly in the context of chronic wound applications.

Most available studies focus on short-term cellular responses under controlled conditions. For instance, the biocompatibility of pure PANI and its derivatives has been extensively investigated *in vitro* across a wide range of cell types, including dental pulp stem cells,²² normal rat fibroblasts,¹⁶⁹ mouse embryo fibroblasts (L929 cells),¹⁷⁰ Schwann cells,¹⁷¹ and cardiomyocytes.¹⁷² Similarly, PPy has demonstrated acceptable cellular tolerance, although mild to moderate cytotoxicity toward NIH/3T3 fibroblasts has been reported.¹⁷³ PEDOT:PSS, in particular, demonstrates excellent biocompatibility with a range of cell lines, including neuroblastoma cells,¹⁷⁴ epithelial,¹⁷⁵ as well as L929 fibroblasts¹⁷⁶ and NIH3T3 fibroblasts.¹⁷⁷ In the NIH3T3, PEDOT showed mild cytotoxicity but did not cause inflammation *in vivo*.¹⁷⁷

However, short-term cytocompatibility does not necessarily predict long-term performance within the complex and hostile microenvironment of chronic wounds. These wounds are characterized by persistent inflammation, elevated levels of ROS, enzymatic activity, and fluctuating pH, conditions that may promote oxidative degradation of conjugated polymer backbones.^{5,178,179} Such degradation can compromise electrical performance and generate low-molecular-weight products with potential biological effects.¹⁸⁰

Among commonly used CPs, PANI is particularly susceptible to overoxidation and pH-induced instability, raising concerns about backbone degradation and the release of aniline or aniline-derived oligomers, which are known to be cytotoxic.^{181,182} Indeed, elevated levels of PANI have been associated with cytotoxic effects and the potential to induce chronic inflammation *in vivo*.¹⁸³ Although PEDOT-based



systems are generally regarded as more chemically stable, challenges such as overoxidation, dopant leaching, and the acidic nature of PSS have been reported, which may affect local tissue responses during prolonged exposure.^{184–186} Collectively, these findings suggest that while CPs demonstrate promising short-term cytocompatibility, their long-term chemical stability and biological safety under chronic wound conditions require further investigation.

Electrical conductivity also varies widely among CPs and directly impacts the efficiency of ES.¹⁸⁷ Researchers have been focused on optimizing the electrical properties of skin scaffolds to match the native conductivity of skin. For instance, pristine silk fibroin (SF) fibers exhibit extremely low conductivity ($1 \times 10^{-11} \text{ S cm}^{-1}$), whereas pure PPy and PANI display much higher conductivities of $1.3 \pm 0.1 \times 10^{-5} \text{ S cm}^{-1}$ and $0.8 \pm 0.1 \times 10^{-5} \text{ S cm}^{-1}$, respectively.¹⁸³ When SF fibers are coated with PPy or PANI, the resulting composites achieve enhanced conductivities of $2.2 \pm 0.1 \times 10^{-5} \text{ S cm}^{-1}$ and $1.6 \pm 0.1 \times 10^{-4} \text{ S cm}^{-1}$, respectively, making coated fibers more suitable for skin tissue engineering.^{183,188} Among the commonly studied CPs, PEDOT:PSS demonstrates the highest conductivity, reaching values around 1–300 S cm^{-1} depending on processing conditions.^{189,190}

Developing a wound dressing with mechanical properties that closely mimic the ECM is essential to avoid structural failures that may compromise cell proliferation and function, and approaches such as polymer blending and surface coating have been widely employed to enhance their mechanical performance.¹⁸³ Nonetheless, fabricating wound dressings using pure CPs presents challenges. These polymers exhibit poor processability and are inherently brittle, making them difficult to manufacture in their pure form.¹⁶⁵

To overcome these limitations, CPs have been chemically modified or physically blended with natural and synthetic polymers.¹⁶⁸ For instance, Xiong *et al.*, (2022) developed a three-layer structure of PPy/polydopamine (PDA)/poly(L-lactide) PLLA, which significantly enhanced conductivity and antibacterial activity. This structure accelerated hemostasis, increased antioxidant capacity, and facilitated the scavenging of ROS. Besides, PPy/PDA/PLLA nanofibers demonstrated excellent biocompatibility and accelerated wound repair in a rat wound healing model¹⁶¹ (Fig. 5).

PANI can also be incorporated into various polymer-based dressings for wound healing and is currently studied in the form of films, hydrogels, or membranes.^{22,162,163} Among these, Moutsatsou and colleagues (2017) developed nanofibrous membranes composed of PANI and CS.¹⁶³ The resulting PANI/CS membranes exhibited excellent cytocompatibility, supporting the adhesion and proliferation of human dermal fibroblasts, even at higher PANI concentrations.¹⁶³

PEDOT has also been combined with biodegradable polymers for the development of advanced wound dressings, designed to enhance healing properties. Alves *et al.*, (2025) reported, recently, electrospun nanofibrous meshes based on PEDOT, CS, and GE, doped with HA. PEDOT incorporation produced porous and biodegradable fibrous meshes with larger

diameters, higher density, reduced porosity, and electrical conductivity.¹⁹¹ Another example of PEDOT use in conductive wound dressings is the combination of PLA with poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), subsequently coated with PEDOT:poly(styrene sulfonate) (PSS). This approach resulted in a conductive membrane that promoted cell attachment and proliferation, and also exhibited no cytotoxicity towards human skin fibroblast cells, highlighting its suitability for tissue engineering applications.¹⁶⁴

These wound dressings have demonstrated significant improvements in the healing of various wound types, such as cutaneous injuries, full-thickness wounds, infected wounds, and diabetic wounds.^{192–195} Furthermore, there are a variety of conductive wound dressings in different forms, including films, membranes, electrospun nanofibers, hydrogels, and foams,^{164,192,193,196,197} with potential for future clinical applications. Currently, no commercially available conductive wound dressings incorporating CPs have been successfully translated for use in wound healing and skin tissue engineering applications.¹⁵⁹ This reflects the early stage of development in this field, where numerous challenges must still be addressed to enable their clinical implementation.

Beyond CPs, other classes of conductive biomaterials have also been explored for wound healing applications, including carbon-based materials (such as graphene and carbon nanotubes) and *meta*-based biomaterials (including silver and gold nanoparticles).^{159,198} While these materials often exhibit higher intrinsic electrical conductivity and, in the case of metals, additional functionalities such as antimicrobial activity, their practical application in flexible and biocompatible wound dressings is limited by potential cytotoxic effects, poor biodegradability, and low mechanical stability.^{199,200} In contrast, CPs offer both adequate electrical conductivity and versatile processability (*e.g.*, electrospinning, coatings, hydrogels), making them particularly well-suited for integration into advanced wound dressings.²⁰¹

5. Synergistic potential of conductive wound dressings and ES

Conductive wound dressings, when combined with electrical therapy, can promote cell migration, alignment, proliferation and differentiation.¹²⁴ This is because they deliver ES more effectively throughout the wound, accelerating wound regeneration and repair.²⁹ It provides an interface that enables homogeneous distribution of the externally applied ES, thereby overcoming the intrinsic limitations of conventional electrode-based stimulation, such as non-uniform current density and localized tissue damage.²¹

Considering that the human body relies on endogenous electrical currents to regulate multiple physiological functions, conductive dressings alone, even without exogenous ES, can exhibit a certain degree of bioactivity by providing cues that guide tissue formation.^{71,202} However, it is the combination with controlled ES that maximizes their therapeutic potential,



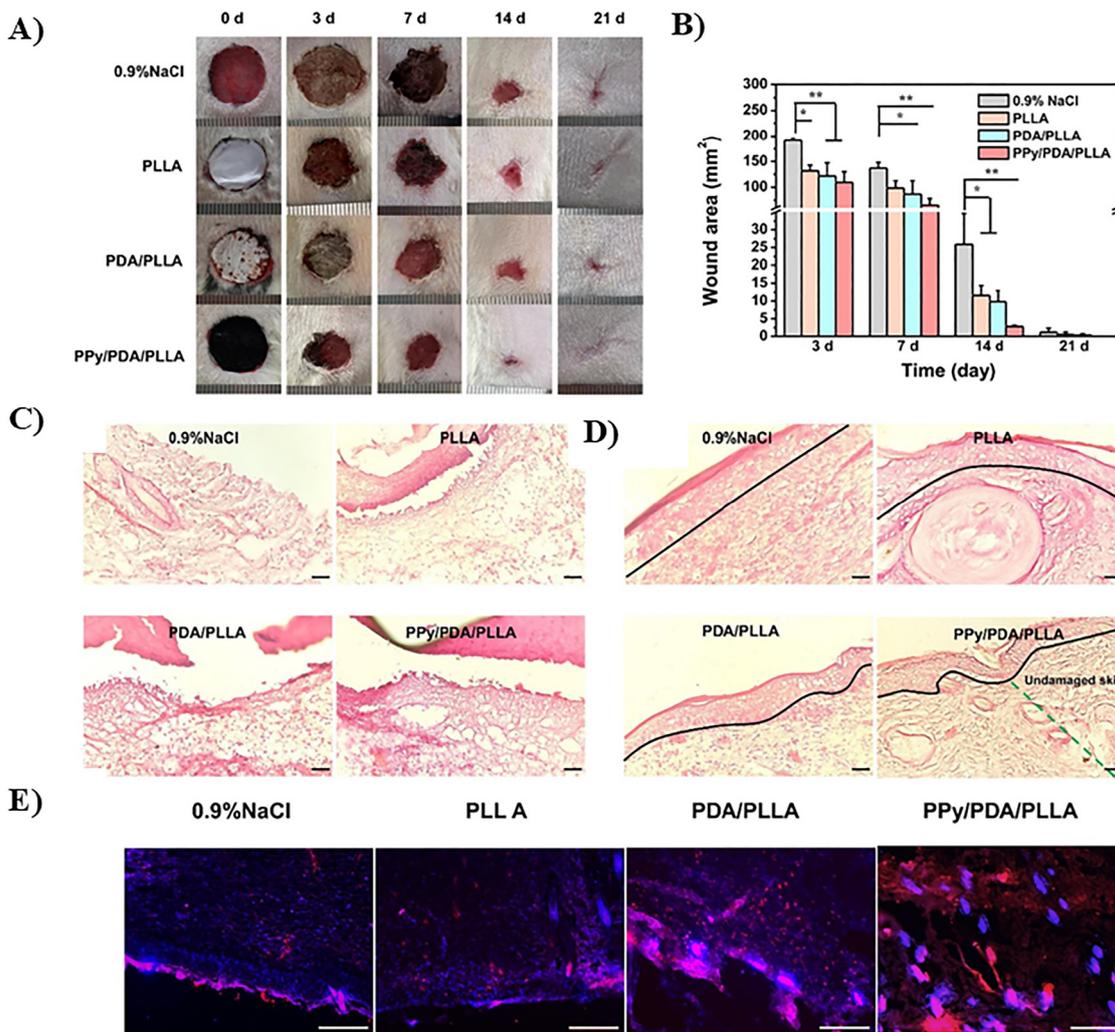


Fig. 5 *In vitro* and *in vivo* evaluation of wound repair using a PPy-based wound dressing. (A) Wound images following treatment with 0.9% NaCl, PLLA, PDA/PLL A, and PPy/PDA/PLL A at days 0, 3, 7, 14, and 21; (B) wound area progression with different treatments; (C) and (D) histological images of tissues from the control and treated wounds on days 3 and 21; (E) Immunostaining for neovascularization (CD31 in red, nuclei in blue) on day 21. Reproduced from ref. 161 with permission from Elsevier, copyright 2022.

as the conductive dressing amplifies the stimulation, resulting in more effective modulation of the wound microenvironment and enhanced healing outcomes.²⁸

While 2D films provide a uniform and continuous conductive interface, electrospun nanofibrous dressings introduce a porous architecture that more closely resembles the skin ECM.^{203,204} Beyond their well-known advantages, as mentioned above, the nanotopography (*i.e.* the nanoscale surface features of individual fibers) of electrospun meshes plays a critical role in modulating electrical interactions at the material–tissue interface.²⁰⁵ The high surface-to-volume ratio and interconnected fiber network increase the effective contact area with cells and interstitial fluids, promoting more distributed charge transfer pathways.^{204,206} In addition, the increased conductive surface area lowers interfacial impedance, allowing electrical currents to pass more efficiently into the tissue.²⁰⁷ These structural and electrochemical characteristics help explain the

improved therapeutic outcomes observed when conductive nanofibrous dressings are used in combination with ES. Indeed, the combination of conductive wound dressings with ES for accelerating wound healing has been supported by several studies,^{21–23,25,30,55,208,209} and is summarized in Table 3. These synergistic effects have been consistently demonstrated in both *in vitro* and *in vivo* models.

Lu *et al.*, (2019) have demonstrated that the application of ES, specifically AC current with varying voltage and frequency, to fibroblast cultures on conductive materials significantly accelerates the wound healing process²¹ (Fig. 6A). *In vitro* assays demonstrated that ES administered to the PPy-based hydrogel enhanced fibroblast migration, with this effect persisting even after ES cessation. *In vivo* studies using diabetic rats showed that ES delivered through a hydrogel resulted in faster wound healing compared to electrode-based ES (Fig. 6B). Similarly, Wu *et al.*, (2021) have developed an intrinsically conductive and



Table 3 Summary of studies on conductive wound dressing combined with ES

Conductive polymer	Dressing components	Dressing form	<i>In vitro/</i> <i>in vivo</i> Studies	Wound type	Exogenous ES	Electrical conductivity/ surface resistivity	Highlights	Ref.
PPy	polyHEMA/ PPY	Hydrogel	Yes/yes	Full-thickness wound	AC at 5 V and 40 Hz for 1 h	N/A	Fibroblast migration and faster wound healing	21
PANI	PAM/SHA/ PANI	Hydrogel	Yes/yes	Infected chronic wound	DC at 3 V for 1 h per day	N/A	Faster wound closure and antimicrobial activity	210
PPy	PPy/PLLA	Membrane	Yes/no	N/A	DC at 50 mV mm ⁻¹ for 4 days	N/A	Enhanced cytokine secretion	25
PPy	PPy/HE/ PLLA	Membrane	Yes/no	N/A	DC at 50 and 200 mV mm ⁻¹ for 2, 4 or 6 h	N/A	Upregulation of fibroblast growth factor secretion	55
PEDOT	PLLA/ PEDOT	Scaffold	Yes/no	N/A	DC at 50 mV mm ⁻¹ for 6 h	0.1 kΩ sq ⁻¹	Supported fibroblast attachment and growth	30
PANI	CPSA-PANI/ PLCL	Nanofibers	Yes/no	N/A	DC, various currents ranging from 0 to 200 Ma for 2 days	0.0015–0.0138 S cm ⁻¹	Enhanced the growth of fibroblasts	208
PPy	PPy/PDLLA	Membrane	Yes/no	N/A	DC, various currents: 0, 5, 10, 50, 100, 200, 400, and 800 μA for 4 days	15–2 × 10 ⁷ Ω sq ⁻¹ (1–17 wt% PPy; threshold 3% ≈ 10 ³ Ω sq ⁻¹)	Enhanced the growth of fibroblasts	209

polyHEMA, poly(2-hydroxyethyl methacrylate); PPy, polypyrrole; PAM, polyacrylamide; SHA, sulfonated hyaluronic acid; PANI, polyaniline; HE, heparin; PLLA, poly(L,L-lactide); PEDOT, poly(3,4-ethylenedioxythiophene); CPSA, camphorsulfonic acid; PLCL, poly(L-lactide-co-ε-caprolactone); PDLLA, poly(D,L-lactide); DC, Direct Current; N/A., not available.

antibacterial hydrogel based on PANI doped with sulfonated hyaluronic acid as a macrodopant. *In vivo* studies demonstrated that ES through this conductive hydrogel enhanced the healing process compared with ES applied *via* conventional electrodes (Fig. 6C). Notably, this combination significantly accelerated

wound healing, with complete wound closure observed within 14 days (Fig. 6D).²¹⁰

ES has also been effectively used to modulate cellular behaviors through membranes or scaffolds. Shi *et al.*, (2008) synthesized PPy/PLLA membranes that supported cell

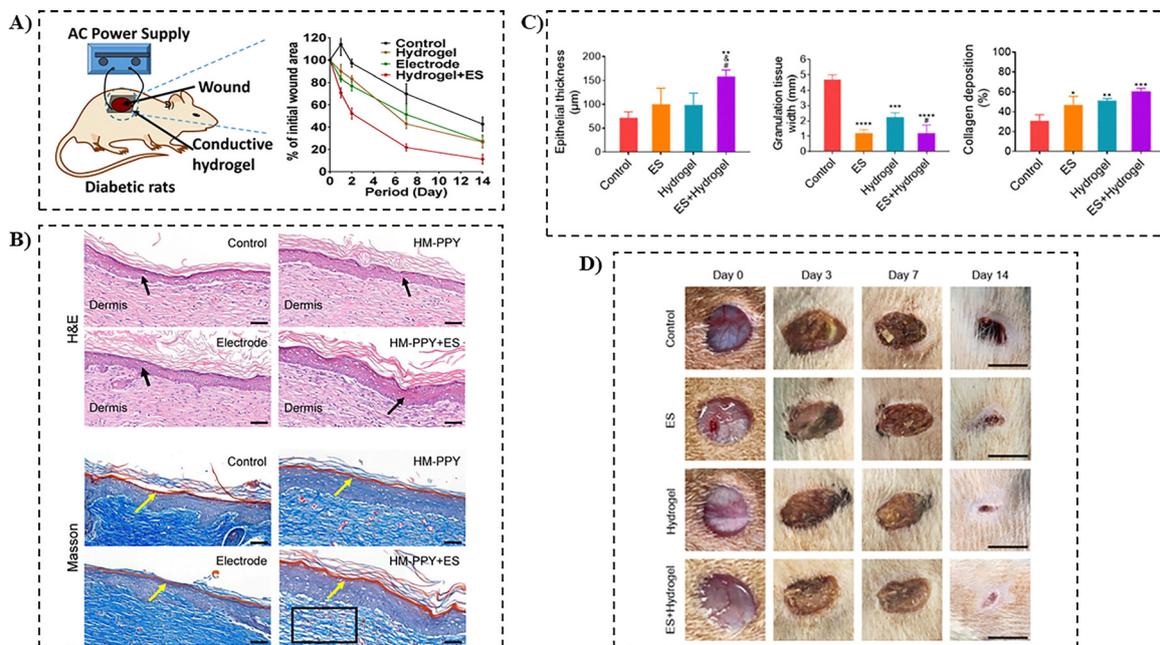


Fig. 6 *In vitro* and *in vivo* evaluation of advanced wound dressings combined with ES. (A) Application of AC *via* a conductive hydrogel on a diabetic rat's wound and its effect on wound closure; (B) histological images of the regenerated tissues. Reproduced from ref. 21 with permission from Elsevier, copyright 2019; (C) evaluation of epithelial thickness, granulation tissue width, and collagen deposition, illustrating the regeneration process; (D) complete wound closure observed within 14 days with the ES and conductive hydrogel. Reproduced from ref. 210 with permission from American Chemical Society, copyright 2021.



adhesion, spreading, and proliferation of human cutaneous fibroblasts both with and without ES (Fig. 7A). Remarkably, the application of a DC electrical field of 50 mV mm^{-1} through these conductive membranes significantly enhanced cytokine secretion compared to controls without ES.²⁵ Additionally, they investigated the impact of ES on human skin fibroblast activity, including myofibroblast transdifferentiation, and its subsequent effects on wound healing.⁵⁵ Human fibroblasts were cultured on heparin-bioactivated PPy/PLLA conductive membranes and subsequently exposed to ES at 50 or 200 mV mm^{-1} for durations of 2, 4, or 6 hours (Fig. 7B).

The application of ES significantly upregulated the secretion of FGF-1 and FGF-2, leading to enhanced cell growth. Interestingly, the beneficial effects of ES persisted even after the cessation of stimulation. Fibroblasts cultured on membranes previously exposed to ES for 4 or 6 hours demonstrated significantly improved growth compared to those cultured on unexposed membranes⁵⁵ (Fig. 7C). The same research group also investigated the application of PEDOT on a conductive scaffold. The resulting PLLA/PEDOT scaffold demonstrated the ability to support fibroblast attachment and growth, which was further enhanced by ES.³⁰ Another study developed by Jeong *et al.*, (2008), delivered ES through PANI-based electrospun nanofibers, enhancing the growth of NIH-3T3 fibroblasts,²⁰⁸ and a similar effect on fibroblast proliferation was observed with DC stimulation delivered through PPy-PDLLA scaffolds.²⁰⁹

More recently, innovative approaches have expanded the synergistic application of ES and conductive dressings. Active wound dressing systems powered by batteries or external power sources provide well-defined and stable electrical outputs, allowing precise control over stimulation parameters such as

current intensity, waveform, and duration.^{211,212} This high level of tunability is advantageous for therapeutic protocols that require reproducible and continuous ES.²¹³ Nevertheless, the integration of external power supplies increases system complexity, device thickness, and overall rigidity, which may compromise patient comfort and long-term adherence.^{137,214} In addition, battery-based systems inherently suffer from limited operational lifetime, requiring recharging or replacement, and may raise safety concerns related to overheating, leakage, or electrical malfunction.^{74,212}

In contrast, passive or self-powered wound dressings, including piezoelectric and triboelectric nanogenerator (TENG)-based systems, rely on biomechanical energy harvesting from patient movement or external mechanical stimuli.²¹⁵ Although the resulting electrical output is typically intermittent and less stable than that of active systems, these devices offer significant advantages in terms of wearability, flexibility, and ease of integration into conventional wound dressings.^{216,217} The absence of batteries or wired connections reduces both maintenance requirements and safety risks, thereby enhancing patient compliance, particularly in long-term or home-based wound care scenarios.^{218,219} From a fabrication standpoint, self-powered systems shift complexity from electronic integration to materials engineering, requiring careful optimization of electroactive layers to ensure sufficient energy generation under physiological conditions.²¹⁵

Overall, while active systems remain advantageous where strict control over ES is essential, self-powered dressings represent a compelling alternative for continuous, low-intensity, and patient-friendly ES. Their inherent simplicity, safety, and potential for long-term operation make them especially attractive for next-generation wearable wound therapies.

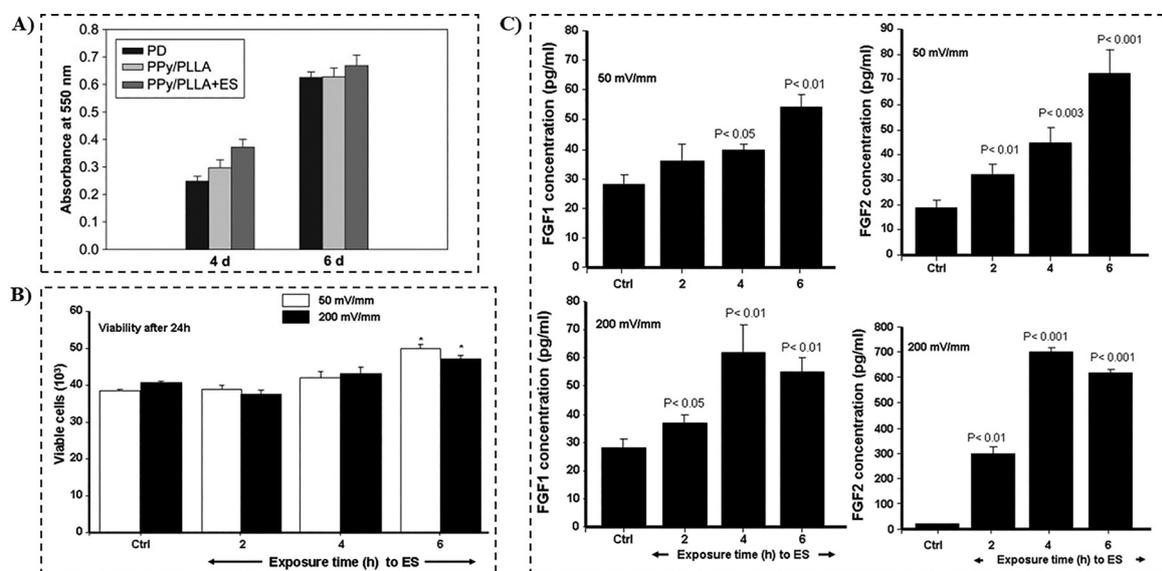


Fig. 7 Effect of ES on human dermal fibroblast and FGF-1 and FGF-2 secretion. (A) Viability of fibroblasts cultured on PPy/PLLA membranes with ES (50 mV mm^{-1}) and without ES for 4 and 6 days. Reproduced from ref. 25 with permission from Elsevier, copyright 2008; (B) viability of dermal fibroblasts cultured on conductive PPy/HE/PLLA membranes with ES at 50 or 200 mV mm^{-1} for 2, 4, or 6 h; (C) effect of ES on FGF-1 and FGF-2 secretion by the dermal fibroblasts with ES at 50 or 200 mV mm^{-1} . Reproduced from ref. 55 with permission from PLOS One, copyright 2013.



In this context, several electrically active electrospun systems have been proposed to deliver localized ES to the wound bed. For instance, magnetoelectric electrospun nanofibers (CoFe₂O₄@CTAB/PVDF) were developed to generate localized ES under magnetic fields, thereby promoting angiogenesis, collagen deposition, and accelerated wound closure in diabetic models (Fig. 8A and B).²²⁰ Similarly, conductive hydrogels based on biological microtubules have been proposed as “natural electrical wires”, to facilitate ES transmission and enhance vascularization, re-epithelialization, and even nerve regeneration in chronic wound models.²²¹ In parallel, a PEDOT-based hydrogel was designed to simultaneously deliver ES and scavenge ROS, significantly accelerating angiogenesis, collagen deposition, and reducing inflammation in diabetic wounds. Additionally, it disrupts bacterial biofilms and enhances antibacterial performance (Fig. 8C).²²²

ES enhances antibacterial activity by affecting bacterial membrane integrity. By altering the membrane potential, the electric field induces pore formation through electroporation, resulting in leakage of intracellular contents and subsequent bacterial death.^{222,225} When combined with conductive nanofibers, which can be designed as wound dressing materials with antibiotics or with antibacterial properties, these effects are amplified.^{144,226} Moreover, the morphology of the nanofibers, particularly the diameter of the fibers, play a significant role in biofilm formation and retention, further influencing the antibacterial efficacy of the dressing.²²⁷

In addition to externally controlled systems, self-powered dressings have emerged as an innovative direction. For example, Barman *et al.*, (2023), developed a multifunctional hydrogel-based dressing integrated with a triboelectric nanogenerator (TEENG) capable of harvesting biomechanical energy from patient movement (Fig. 8D). This approach eliminates the need for external power sources while simultaneously reducing bacterial load and accelerating wound closure in infected wound models (Fig. 8E).²²³ Similarly, a PEDOT-incorporated GE hydrogel functionalized with polydopamine demonstrated that conductive scaffolds can improve fibroblast migration and antioxidative capacity, with and without exogenous ES, highlighting the intrinsic bioactivity of electroactive materials.²²⁸

Furthermore, the integration of therapeutic and diagnostic functionalities has also been explored. A conductive nanofibrous membrane incorporating Ag/Zn electrodes was shown to deliver ES while enabling temperature monitoring, thus providing real-time feedback on inflammatory responses and paving the way for “smart” wound dressings (Fig. 8F).²²⁴

While these examples demonstrate the potential of self-powered and smart electrically active wound dressings, they also reveal important engineering and safety challenges that must be considered for clinical translation. In triboelectric and piezoelectric-based systems, long-term durability under repetitive mechanical deformation and patient movement remains a key issue, as material fatigue may lead to unstable electrical output.^{212,229} Similarly, magnetoelectric platforms require careful control of externally induced fields to avoid localized hotspots at the wound-device interface.²¹¹ Moreover, the

integration of sensing functionalities introduces challenges related to sensor reliability, signal stability, and calibration in dynamic and moist wound environments.^{211,212,220} Addressing these issues will be essential to ensure safe, robust, and clinically relevant next-generation electrically active wound dressings.

6. Challenges and critical perspectives on clinical translation

The clinical use of ES devices is subject to regulatory oversight to ensure safety and efficacy, with approvals varying on the intended therapeutic application. While the FDA has granted premarket approval for ES applications in bone regeneration, deep brain stimulation, and muscle stimulation, there is still no specific approval for wound healing.⁷⁹ Despite this, ES therapy has been successfully applied ‘off-label’ in clinical practice as an adjunctive treatment for pain management and wound healing, including both chronic and acute wounds, as supported by numerous studies.^{14,20,103,230–232} However, clinical trials remain scarce and highly heterogeneous, with considerable variability in parameters such as polarity, current density, frequency, and stimulation duration. This lack of standardization complicates the establishment of consistent therapeutic protocols and hinders direct comparison of outcomes across studies.

Another significant challenge relates to material stability and safety. While conventional wound dressings are typically composed of FDA-approved synthetic and natural polymers, which are generally regarded as safe, the situation is more complex for conductive biomaterials. CPs, despite their promising electrical properties, may undergo structural or chemical degradation under physiological conditions, resulting in reduced conductivity, loss of functionality, or even local toxicity.²³³ Moreover, their long-term biocompatibility and degradability *in vivo* remain uncertain, highlighting the need for further systematic studies to establish their safety for clinical translation.

In addition, manufacturing and reproducibility remain critical challenges for electrospun conductive dressings. Electrospinning is highly sensitive to process parameters, which can lead to batch-to-batch variability in fiber diameter, CP loading, and overall conductivity.^{234,235} Such variations can influence not only mechanical and structural properties but also electrical performance, complicating the development of standardized therapeutic protocols.²³⁶ Standardization of electrospinning parameters, rigorous quality control, and integration of sterilization-compatible production methods are therefore essential to ensure reproducible and clinically translatable dressings.

Moreover, sterilization processes may further increase these inconsistencies, further affecting fiber morphology or CP distribution. Developing sterilization strategies that maintain both the structural integrity and electrical functionality of multi-component conductive dressings is therefore essential for clinical translation. Methods such as low-temperature plasma sterilization or ethylene oxide treatment could offer potential



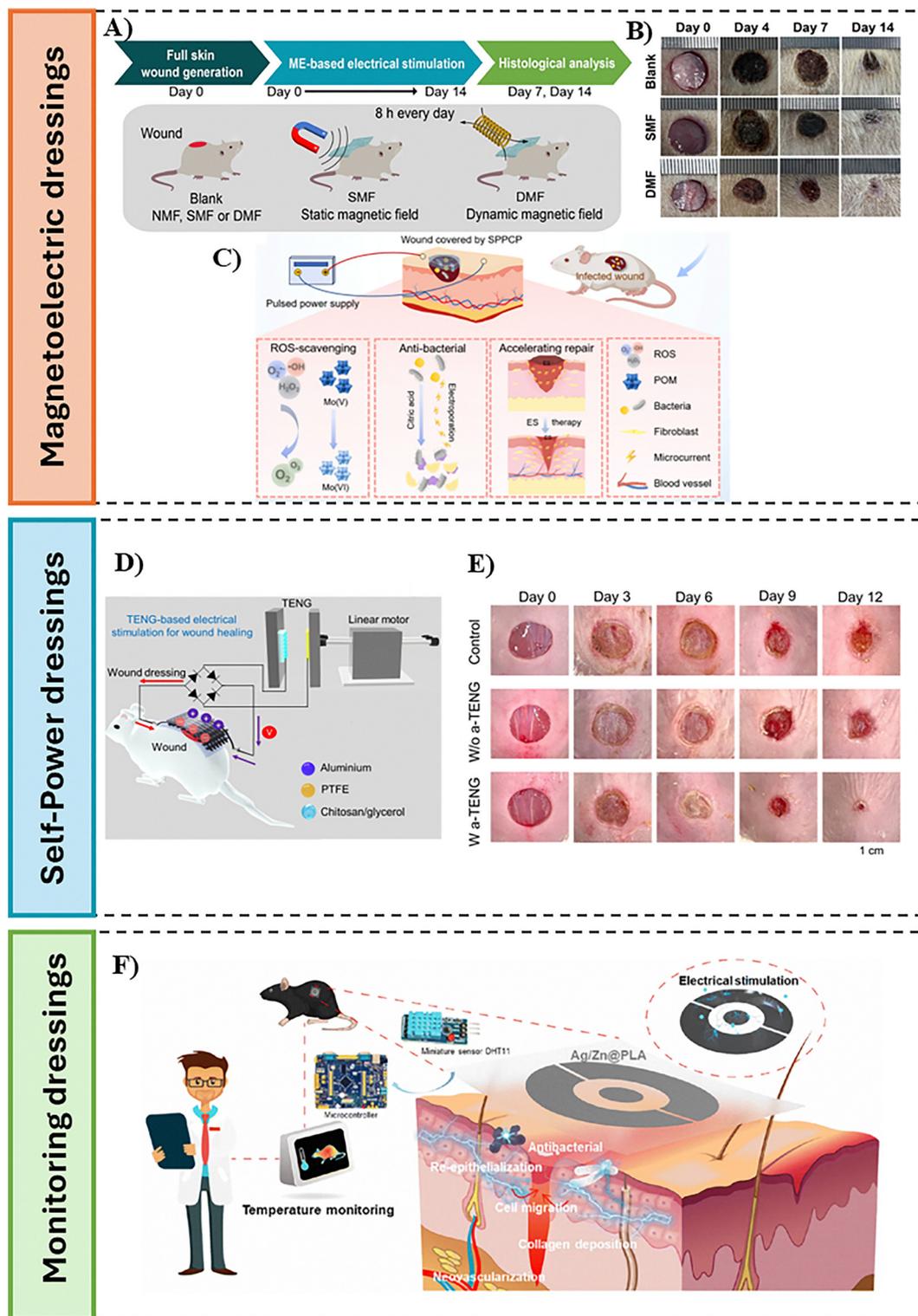


Fig. 8 Representative examples of emerging categories of conductive wound dressings. (A) Experimental scheme of magnetolectric wound dressings applying static (SMF) or dynamic magnetic fields (DMF) to induce localized ES. (B) Macroscopic images of wound healing progression under blank, SMF, and DMF conditions from day 0 to day 14. Reproduced from ref. 220 with permission from American Chemical Society, copyright 2024; (C) Schematic of the SPPCP (molybdenum-based CD-POM) dressing illustrating its multifunctional effects. Reproduced from ref. 222 with permission from Elsevier, copyright 2025. (D) Self-powered dressing based on a triboelectric nanogenerator (TENG) coupled to wound sites for autonomous ES delivery. (E) Photographs of wound closure over 12 days in control, with and without-TENG groups, showing accelerated healing in the TENG-integrated system. Reproduced from ref. 223 with permission from American Association for the Advancement of Science (AAAS), copyright 2023. (F) Schematic of a smart monitoring dressing integrating temperature sensors and a conductive Ag/Zn@PLA platform. Reproduced from ref. 224 with permission from Royal Society of Chemistry, copyright 2023.



solutions, but their effects on conductivity, mechanical properties, and biocompatibility need rigorous analysis.^{237,238}

To date, conductive electrospun wound dressings have not received FDA approval, largely due to insufficient clinical evidence demonstrating their long-term safety, efficacy, and reproducibility. From a regulatory perspective, devices that combine scaffolds with active ES are considered “combination products”, which require a coordinated evaluation of both the scaffold material and the electrical component.²¹¹ In the United States, such products are typically reviewed by the FDA, with the Center for Devices and Radiological Health (CDRH) leading the assessment for device functions, and the Center for Biological Evaluation and Research (CBER) involved if biologically active components are present. Regulatory pathways may include a 510(k) premarket notification if a predicate device exists, or a full Premarket Approval (PMA) for novel designs. Required testing encompasses biocompatibility, controlled degradation, electrical safety, and electromagnetic compatibility (EMC) to ensure patient safety and device reliability.^{211,239} In the European Union, these products are regulated under the Medical Device Regulation (MDR, Regulation (EU) 2017/745), with oversight from the European Medicines Agency (EMA).²³⁹ These combination devices are generally classified as class IIb or III based on risk.²¹² CE marking requires assessment by a Notified Body, which evaluates not only electrical safety and EMC, but also scaffold degradation, biocompatibility, risk management, and detailed technical documentation, including quality control and manufacturing consistency.^{212,240}

Animal models used in preclinical testing often fail to fully replicate the complexity of human chronic wounds, particularly under conditions such as diabetes or venous insufficiency. This raises concerns about the predictive validity of preclinical data and contributes to the translational gap between experimental findings and clinical outcomes. Species differences must be considered, as studies on conductive fiber scaffolds in wound healing predominantly utilize rats, largely due to their convenience and cost-effectiveness. However, significant differences between rats and humans in skin structure, immune response, and metabolic rate can limit the translatability of experimental results to clinical practice. For this reason, large animal models, such as pigs, which more closely resemble the structural and physiological properties of human skin, should be prioritized in future studies.

Clinical translation of electrically active wound dressings has so far been limited to electroceutical systems such as Procellera[®] (Zn/Ag microcell arrays), PosiFect[®] RD (microcurrent-generating dressings), and Accel-Heal[®] (integrated low-voltage pulsed current devices). A drawback of these electroceutical systems lies in their non-biodegradable nature, which necessitates removal or replacement after use. This contrasts with conductive wound dressings, which are designed to be biodegradable and bioresorbable, allowing them to gradually degrade *in situ* while maintaining therapeutic function, thereby reducing the need for dressing changes and minimizing patient discomfort. Nevertheless, most evidence is derived from small, heterogeneous trials or case series, often

without standardized stimulation protocols. Importantly, while these dressings exemplify the feasibility of combining exogenous ES with wound coverings, they rely on metallic electrodes or galvanic reactions rather than conductive electrospun nanofibers.

To date, no randomized controlled trial has evaluated the synergistic use of conductive electrospun dressings with controlled ES in human patients. This gap underscores a major translational challenge: although preclinical studies consistently demonstrate enhanced cell migration, angiogenesis, and accelerated healing with electrospun conductive dressings under ES, clinical validation remains absent. Bridging this gap will require large-scale, well-designed clinical trials, harmonization of ES parameters, and rigorous assessment of long-term safety and biocompatibility of conductive polymers in humans.

7. Conclusion and future perspectives

Chronic wounds continue to pose a significant global health challenge, demanding innovative and effective therapeutic approaches to address their complex pathology and suboptimal healing outcomes. ES has shown promise in accelerating wound healing, but traditional electrode-based approaches face limitations in delivering uniform and controlled stimulation. Conductive electrospun-based wound dressings offer a transformative platform by combining biomimetic ECM structures with the capacity to apply ES at the wound site. This synergy has demonstrated enhanced healing outcomes and addressed the limitations of each therapy when used independently. Despite promising preclinical results, further *in vivo* studies are needed to fully elucidate the interactions between ES and conductive dressings.

Research consistently demonstrates that conductive dressings combined with ES hold significant promise for wound healing. However, their clinical translation remains hindered by critical challenges, including the lack of standardized ES parameters, regulatory hurdles associated with conductive materials, and the need for comprehensive biocompatibility and efficacy studies, especially in animal models with skin more comparable to humans. Addressing these challenges through interdisciplinary research and technological advancements will be the key to developing more effective and clinically applicable wound healing solutions. Moreover, the predominantly two-dimensional structure of electrospun dressings limits their use in deep chronic wounds, where three-dimensional scaffolds are necessary to support cell infiltration and vascularization. Future research combining electrospinning with complementary fabrication techniques may overcome these challenges. By addressing these gaps, the integration of ES with conductive nanofibrous dressings has the potential to revolutionize chronic wound management, improving patient outcomes and reducing the healthcare burden.

Author contributions

JL wrote the manuscript, designed and illustrated the figures and tables. MTC, FR, and JRD supervised, edited, and approved



the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Acknowledgements

This work was financed by National Funds through FCT/MCTES – Portuguese Foundation for Science and Technology within the scope of the project UIDB/50006/2025 (<https://doi.org/10.54499/UID/50006/2025>) and CDRSP funding (DOI: 10.54499/UID/04044/2025), ARISE funding (DOI: 10.54499/LA/P/0112/2020); and the contract funding to Juliana Dias (10.54499/CEECINST/00060/2021/CP2902/CT0005). This study was also supported by Nanofilm (CENTRO2030-FEDER-01469100).

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