

# Healing Chronic Wounds From Electric Stimulation

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**Abstract:** *Electrical stimulation (ES) has gained considerable attention as a therapeutic modality for enhancing the repair of chronic wounds. By reproducing the body's endogenous electric fields, ES modulates several biological processes, including directed cell migration, angiogenesis, collagen remodeling, antibacterial activity, and the proliferation of keratinocytes and fibroblasts. Different stimulation formats such as direct current (DC), alternating current (AC), and pulsed current (PC) have demonstrated measurable improvements in tissue regeneration by regulating ion transport and activating intracellular signaling pathways. Recent advances in self-powered electroactive systems, including enzymatic biofuel cells, piezoelectric and triboelectric nanogenerators, conductive polymers, and electroconductive hydrogels, offer sustained local stimulation without the need for external energy sources. This review synthesizes current knowledge on the mechanisms, device platforms, and therapeutic potential of ES for chronic wound management and highlights its emerging role in restoring bioelectric cues essential for effective healing.*

**Keywords:** Wound healing, Chronic wounds, Electrical stimulation, Electric field

## I. INTRODUCTION

The epidermis and dermis are the protective layers of cells that make up skin, together with their secretions. The cells of the epidermis and dermis, as well as their secretions, are necessary to form a semipermeable barrier against different microbes.[1] The basement membrane, a highly specialized extracellular matrix (ECM), connects these two opposing layers. The dermis provides the epidermis with nutrients and mechanical stability. The interdigitating arrangement of dermal protrusions (papillae) within the epidermis and epidermal downgrowths (rete ridges) within the upper dermis improves both by providing an overall larger junction surface.[2]

Wound healing is a very complicated biological process that occurs when the skin's barrier function is impaired due to burns, surgery, unintentional injuries, skin disorders, microbial infections, or metabolic dysfunction.(1) Wound healing is essential for human health as it is necessary for the restoration of damage to skin or organs.Wound healing is a complicated process involving several interconnected physiological processes such as inflammation, proliferation, and remodeling.[3]

The body's natural response to tissue damage is wound healing. However, the vascular system, cytokines, mediators, and a variety of cell types interact intricately during wound healing, making it a complex process. The initial cascade of platelet aggregation and blood vessel vasoconstriction is intended to halt bleeding. A flood of different inflammatory cells, beginning with the neutrophil, follows. A range of mediators and cytokines are then released by these inflammatory cells to encourage thrombosis, angiogenesis, and reepithelialization. In turn, the fibroblasts deposit materials beyond the cell that will act as scaffolding.[4] Hemostasis, chemotaxis, and enhanced vascular permeability are characteristics of the inflammatory phase that prevent more damage, seal the wound, eliminate bacteria and cell debris, and promote cellular migration. The inflammatory stage typically lasts for a few days. Granulation tissue development, reepithelialization, and neovascularization are characteristics of the proliferative phase. This stage may continue for a few weeks. The wound reaches its maximal strength throughout the maturation and rebuilding stages.[5]



**Phases Of Wound Healing:**

**Inflammatory Phase (Hemostatis and Inflammation):**

Vascular constriction and platelet aggregation start hemostasis to stop blood loss as soon as tissue damage occurs. Inflammatory cells are drawn to platelets because they emit growth factors and clotting factors including transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).

**Proliferative Phase (Granulation and Re-epitheliazation):**

In order to fill the wound space, new tissue must form during this phase. Collagen type III and extracellular matrix (ECM) components are produced by fibroblasts that move to the wound. Vascular endothelial growth factor (VEGF) stimulates angiogenesis, which results in the production of granulation tissue.

**Remodeling (Maturation) Phase:**

Collagen type I replaces the initially deposited collagen type III in this last stage, increasing the wound's tensile strength. As the granulation tissue develops into a scar, the vascular density falls.[6]

Phase	Time Frame	Cells	Etiology
Inflammatory	0-3 Days	Neurophilis, Macrophages.	Hemostatis, Inflammation, Debris Removal.
Proliferative	3-10 Days	Fibroblasts, Endothelial Cells, Keratinocytes.	Granulation Tissue, Angiogenesis, Re-epitheliazation.
Remodeling	1 Weak-1Year	Fibroblasts, Microfibroblasts.	Collagen remodeling, Scar formation.

Table.1 Phases Of Wound Healing.

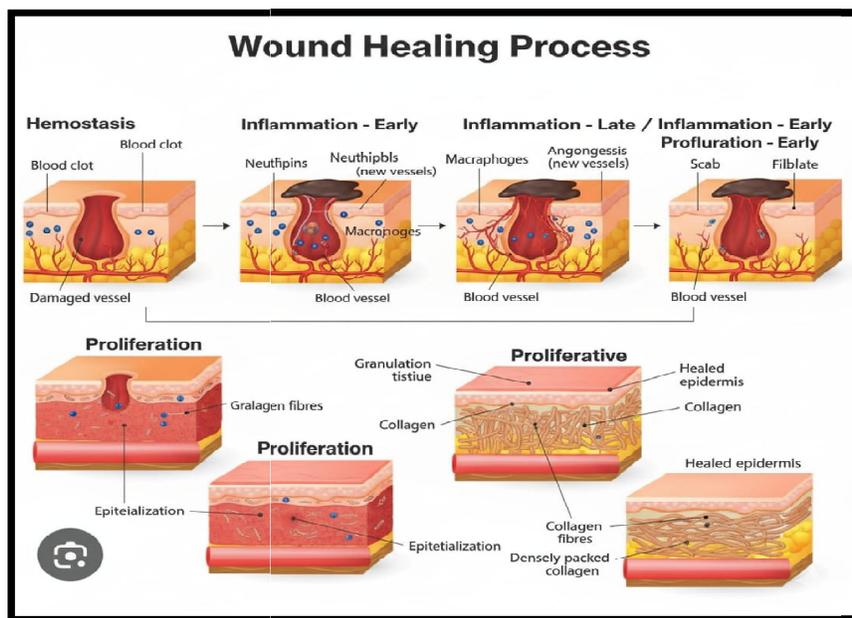
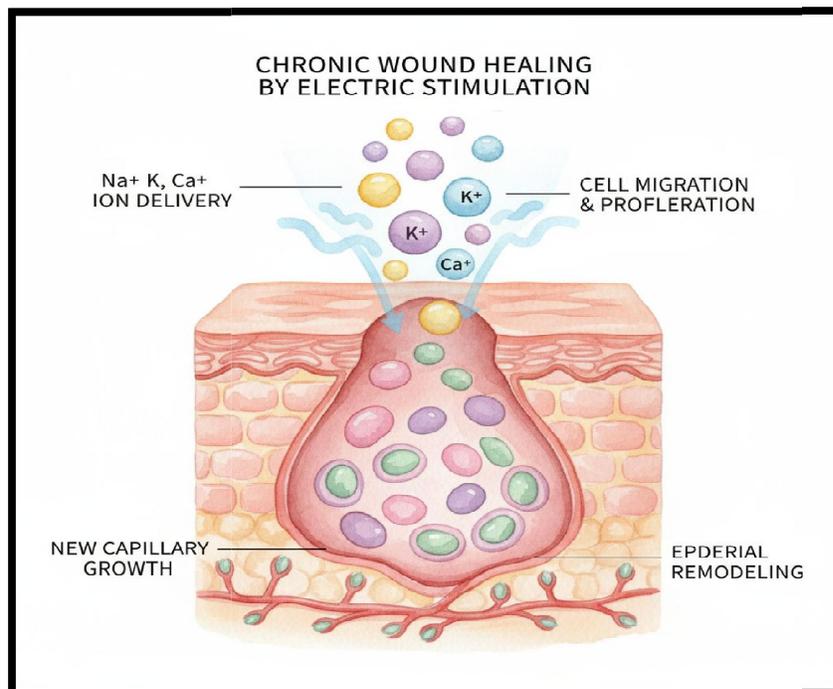


Fig.1 Wound Healing Process



skin maintains a surface potential that is negative in comparison to that beneath the skin. An endogenous electric potential and a transcutaneous potential of 20–50 mV are maintained by healthy, undamaged human skin. The epidermis's active Na<sup>+</sup>/K<sup>+</sup> ATPase pumps produce and maintain this. Ion leakage across damaged cells or cell layers happens after injury. This creates a voltage gradient that is laterally oriented at wounds and points toward the center of the wound. The endogenous electric potential is produced by the asymmetric ionic fluxes of mobile charged ions. The primary constituents of the endogenous electric currents are Na<sup>+</sup>, Cl<sup>-</sup>, K<sup>+</sup>, and Ca<sup>2+</sup>. The electric field drives ions like sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>), and calcium (Ca<sup>2+</sup>) across cell membranes, enhancing cellular signaling and protein synthesis. ES also influences the electrode-tissue interface, causing local pH shifts and electrochemical reactions that stimulate cell growth and aid in reducing infection by altering bacterial cell membranes.[7]



**Fig.2 Ion exchange during healing wounds.**

## II. LITERATURE REVIEW

**R. K. Thapa, Diep & Tonnesen (2020)**, Topical antimicrobial peptide formulations for wound healing.

Antimicrobial peptides (AMPs) show strong potential for treating infected and chronic wounds because they not only kill bacteria but also promote tissue repair. However, their direct application is limited by rapid degradation caused by wound enzymes, pH variations, and poor inherent stability. The review highlights recent progress in topical AMP delivery systems such as hydrogels, nanoparticles, creams, and wafer-based formulations which protect AMPs from breakdown, enhance their stability, and enable controlled release at the wound site. These advanced formulations improve antimicrobial effectiveness and accelerate wound healing in preclinical models.

**Nuccitelli, R. (2003)**, A Role for Endogenous Electric Fields in Wound Healing.

Nuccitelli reviews experimental evidence that natural (endogenous) electric fields play a significant role in the process of wound healing in vertebrates. When epithelial tissues (like skin) are wounded, their normal voltage gradients are disrupted, creating lateral electric fields around the injury. These fields have been measured in several systems, and typical strengths lie between about 40–200 mV/mm. Many cell types important for healing such as human



keratinocytes can sense these physiological-strength fields and move directionally (a behavior called electrotaxis). Their response depends on calcium influx, specific growth factors, and certain intracellular kinases: for instance, protein kinase C is needed in neural crest cells; cAMP-dependent kinases in keratinocytes; and MAP (mitogen-activated) kinase in corneal epithelial cells

**Guangping Tai, Min Zhao (2018)**, Electrically stimulated cell migration and its contribution to wound healing.

Electric fields strongly influence and even override other cues to control the direction of cell movement. Because of this ability, electrical stimulation (ES) is emerging as a promising therapeutic approach to enhance wound healing, especially in chronic or non-healing wounds. The review highlights current understanding of how electric fields function at physiological, cellular, and molecular levels, discusses their therapeutic applications, and identifies remaining questions that need further research.

**Tae-Hyun Kim, Yunseong Ji(2021)**, Electricity auto generating skin patch promotes wound healing process by activation of mechanosensitive ion channels.

The study shows that a glucose-powered enzymatic biofuel cell (EBC) skin patch can generate electricity at the wound site and significantly speed up healing. It reduces inflammation, enhances angiogenesis, and improves fibroblast and matrix activity. These effects occur through calcium influx mediated mainly by the mechanosensitive ion channel Piezo1. Blocking Piezo1 reduces the healing benefits, suggesting EBC patches as a promising wound-healing device.

**Sivaraj Mehnath(2025)**, Recent advances in polysaccharide-derived piezoelectric nanogenerators for wound healing application.

The article reviews how polysaccharide-based piezoelectric nanogenerators can serve as self-powered wound-healing devices. These materials convert natural body movements into gentle electrical signals that promote cell growth and tissue repair. Polysaccharides are highlighted because they are biocompatible, flexible, and can be engineered to improve electrical output. The review also explains recent material designs, their benefits for faster healing, and current challenges such as stability and performance optimization.

**Karthikeya Venugopal et al,(2021)**, Comprehensive Review on Triboelectric Nanogenerator Based Wrist Pulse Measurement: Sensor Fabrication and Diagnosis of Arterial Pressure.

The paper reviews how triboelectric nanogenerators (TENGs) can be used as self-powered sensors to measure wrist pulse and estimate arterial pressure. It explains how different materials, surface structures, and device designs improve sensitivity and signal quality. The authors highlight that TENG-based sensors are lightweight, low-cost, and do not need external power, making them suitable for continuous health monitoring. The review also discusses how pulse signals captured by TENGs can help assess cardiovascular conditions and outlines challenges such as improving durability, stability, and data accuracy.

**Subham Preetam et al, (2024)**, Electrical stimulation: a novel therapeutic strategy to heal biological wounds.

This review discusses how low-intensity electrical stimulation (ES) can enhance wound healing by speeding up tissue repair. ES helps wounds close faster, reduces inflammation, boosts new blood vessel formation, and stimulates cell migration and growth. The authors examine different ES types (direct current, alternating current, pulsed) and their biological effects, explaining how electrical signals interact with cells via ion transport, cytoskeleton remodeling, and cell signaling. They also highlight the potential of ES as an adjunct treatment for difficult wounds (like chronic or diabetic ulcers) and call for more research to optimize stimulation parameters and device designs for safe and effective clinical application.



**Background:**

The application of electric field (EF) energy to promote healing in chronic wounds has been utilized for many years and relies on the presence of natural wound EFs that have been noted to guide cell movement following an injury to the skin. (7) The magnitude of endogenous wound electric fields (EFs) measured in both animal models and humans, which have been observed to guide cell migration (electrotaxis) following injury, has been quantified within the range of 10 to 100  $\mu\text{A}/\text{cm}^2$ . Prior research has demonstrated that EF energy facilitates the migration of various cell types, including lymphocytes, fibroblasts, macrophages, and keratinocytes. Moreover, in chronic, non-healing wounds, it is plausible that the endogenous EFs are either disrupted or absent, which often correlates with a lack of response to standard wound care (SWC). In instances where SWC alone is insufficient to promote healing in chronic wounds, the adjunctive use of electrical stimulation (ES) alongside SWC has been shown in multiple clinical trials to improve wound healing and closure outcomes. Subsequent sections of this work will provide detailed analyses of these studies. The current discussion aims to clarify ES-related terminology, describe the various types of ES energy and signal parameters reported to enhance wound repair, and elucidate the methods by which ES is applied to wounds. Additionally, prospective developments in ES technology for wound healing will be explored.[8]

**Exogenous electric field:**

Exogenous electric fields typically function by mimicking and enhancing wound potential through the use of external electric stimulation. The primary claims that numerous electrical stimulation devices have been created and extensively used in tissue engineering and wound healing. Electrodes can be classified into two groups based on the various areas where they act on the wound. In particular, the unidirectional current or voltage occurs when the anode is placed on healthy skin close to the wound and the cathode is placed in the center of the wound; the bidirectional current or voltage occurs when two electrodes are placed on healthy skin on either side of the wound. Common electrical energy-supplying methods for electrical stimulation are DC and PC. DC's capacity to influence the directional migration of epithelial cells has shown it to be a highly promising contender.[10]

**Endogenous electric field:**

The short circuits of a trans-epidermal potential (TEP) are responsible for the electric current generated at wound sites. TEP is specifically created by directed ion transport (sodium, potassium, and chloride ions) through polarized epithelial cells and the asymmetric distribution of ion channels in the epithelial layer. It was shown that the direction of positive charge flow was determined by the wound center. Additionally, injured skin exhibits a negative potential when compared to healthy skin. This indicates that the production of a lateral endogenous electric field is encouraged by the appearance of a potential gradient, which causes current to flow from the normal skin at a specific distance away from the wound toward the wound. It has been shown that modifying ion transport can have a positive impact on wound healing. Endogenous ionic currents are hence crucial guidance cues in the healing of wounds.[11]

**Current:**

Electric current (I) is defined as the rate at which charged particles, such as electrons or ions, pass a given point in a specified direction. In metallic wire conductors, current is carried by the movement of electrons, whereas in biological tissues, current flow is mediated by ions, including sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ), and chloride ( $\text{Cl}^-$ ). The standard unit of electric current is the ampere (A), which quantifies the rate of charge flow past a fixed reference point within a conductor. Mathematically, current is expressed as  $I = C/t$ , where I represents current in amperes, C denotes charge in coulombs, and t corresponds to time in seconds. One ampere is equivalent to one coulomb of charge passing per second. While coulombs measure the quantity of electrons, amperes indicate the rate at which these electrons flow. Externally applied currents to wounds, designed to replicate physiological direct current (DC) tissue currents, typically exhibit magnitudes ranging from one-thousandth to one-millionth of one ampere, situating them within the milliampere (mA) to microampere ( $\mu\text{A}$ ) scale. When unidirectional direct current (DC) or pulsed current (PC) is administered to a



wound via electrodes, active cells involved in the healing process—such as neutrophils, macrophages, fibroblasts, and keratinocytes—may migrate directionally in response to anodal or cathodal polarized electric fields, a phenomenon known as electrotaxis. Additionally, fibroblasts may experience upregulation, resulting in an increased rate of DNA synthesis.[12]

**Type of exogenous wound healing current:**

**Low- intensity direct current(LIDC) :**

Low-intensity direct current (LIDC) has been investigated as a basis for antimicrobial treatments utilizing electrochemical ionization mechanisms. our research group has developed several configurations of LIDC-stimulated oligodynamic metal ion-based technologies applicable to orthopedic implantable medical devices. These system configurations operate under electric currents up to 20  $\mu$ A and function either prophylactically to prevent infection onset or therapeutically to eradicate infections once detected. The underlying concept of this technology, along with its demonstrated efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA), has been documented. The ionization effect induced by these systems can be quantitatively described using Faraday's law of electrolysis.

**High voltage pulsed current(HVPC) :**

High-Voltage Pulsed Current (HVPC) is characterized as a monophasic pulsed electrical stimulus comprising double-peaked impulses with durations ranging from 5 to 200 microseconds. It operates at a notably high peak current amplitude between 2 and 2.5 amperes and a voltage reaching up to 500 volts, delivered at frequencies spanning 1 to 125 pulses per second. HVPC has been demonstrated to activate the “skin battery” mechanism and facilitate cellular galvanotaxis, thereby enhancing blood circulation and increasing capillary density.

**Pulsed current(PC) :**

Pulsed current refers to a discontinuous flow of charged particles characterized by a series of pulses interspersed with intervals of no current flow. During each pulse, the current may either flow unidirectionally, termed monophasic pulsed current, or bidirectionally, referred to as biphasic pulsed current. Monophasic pulsed currents are applicable to various clinical electrical stimulation treatments; however, they are predominantly employed to facilitate tissue healing and manage acute edema.

**Direct current(DC) :**

Direct current (DC) can be used in healing by applying external electrical fields to stimulate natural cellular processes that occur during tissue repair. The body naturally has a DC bioelectric system, and external DC stimulation can encourage wound closure by promoting cell migration (galvanotaxis), which helps re-establish the necessary cellular structure. It is used in treating chronic wounds and can accelerate healing in both healthy and unhealthy skin models.

**Alternating current (AC) :**

Alternating current stimulation (ACS) is a non-invasive neuromodulation technique that has been comparatively less explored than transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). Although ACS employs the same equipment and electrode configurations as tDCS, it utilizes distinct current waveforms. The stimulation waveform varies cyclically over time, typically consisting of sinusoidal or square pulses that traverse the skull via electrodes positioned on the scalp surface or are transmitted through the eye and optic nerve to reach the brain. Electrode placement can be tailored according to the targeted brain region, referred to as transcranial placement, or positioned adjacent to the eyes, known as transorbital placement. The neuronal effects elicited by ACS are highly dependent on stimulation parameters, including current density, frequency range, electrode size, and electrode positioning.



**Electroceutical devices:**

Externally administered electrical signals engage with biological tissues at an electrochemical level by influencing ion transport, the electrode–tissue interface, and the polarization of cellular membranes. These combined effects are believed to reestablish the intrinsic bioelectrical signals essential for optimal wound repair. Specifically, electrical stimulation facilitates the transmembrane movement of ions such as  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$ , thereby promoting intercellular communication, protein synthesis, and intracellular signaling pathways, which collectively expedite the healing process.

**Enzymatic biofuel cells (EBFCs) :**

Enzymatic biofuel cells (EBFCs) are a type of electrochemical device for converting chemical energy into electricity . Enzymatic biofuel cells (EBFCs) use oxidoreductase enzyme commonly ‘Glucose oxidase’ at the anode and ‘Laccase or Bilirubin oxidase’ at the cathode. Generate microcurrents that stimulate cell migration and accelerate healing. EBFCs can also be utilized for self-powered therapeutic systems by delivering direct electrical stimulation or by releasing drugs in a controlled manner. EBFC is a potential platform for diagnostics and treatments because to its additional self-powered sensing and treatment capabilities. Resolving EBFC’s restricted power density and longevity can be the main focus of future efforts.(13)

**Mechanism:**

**Galvanotaxis and electrotaxis:**

Keratinocytes, fibroblasts, and endothelial cells migrate according to endogenous electrical gradients. These bioelectric cues are mimicked or enhanced by EBFC-generated microcurrents, which encourage directed cell migration (re-epithelialization) and quicker wound closure. EBFC-generated fields have been shown to improve cell migration and viability in a number of in vitro and in vivo investigations.

**Angiogenesis and proliferation:**

Local electric fields can enhance the creation of granulation tissue by upregulating angiogenic signaling, endothelial cell activity, and fibroblast proliferation. In patch studies and animal models, EBFC-driven microcurrents have been linked to increases in proliferation markers.

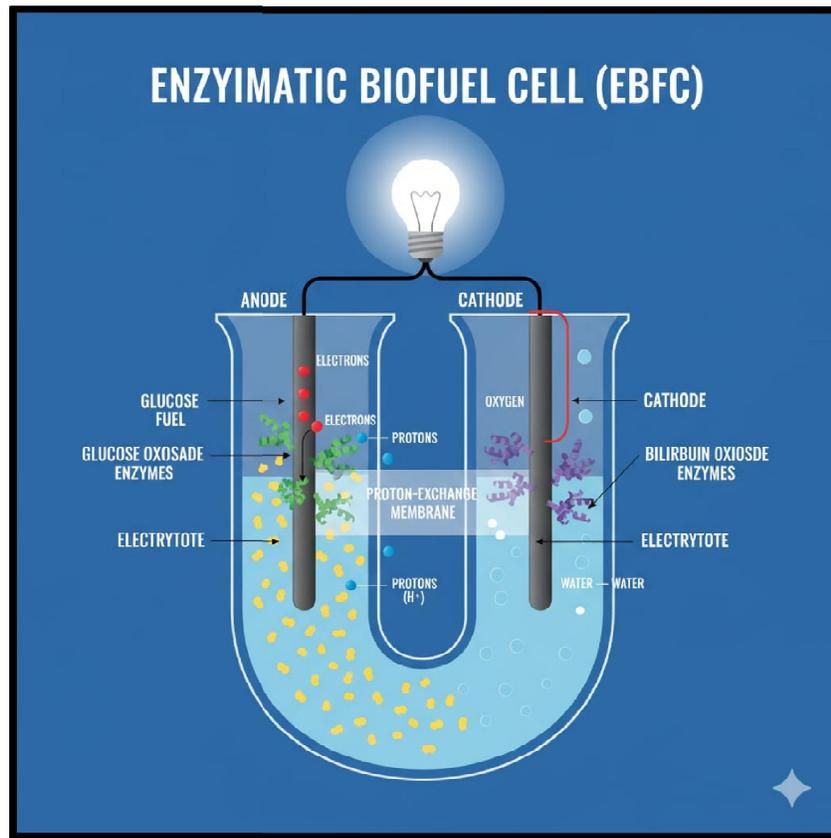
**Consumption of glucose and local metabolic changes:**

Local glucose depletion can partially regulate the environment and lessen glucose-driven glycation/stress in diabetic wounds when hyperglycemia in exudate hinders healing. This is because GOx/GDH utilize glucose in the wound microenvironment. This is one suggested method for advantages that go beyond only power.

**Reactive oxygen species (ROS) and  $\text{H}_2\text{O}_2$ :**

GOx reduces  $\text{O}_2$  to  $\text{H}_2\text{O}_2$  and oxidizes glucose to gluconic acid. Some EBFC designs purposefully take advantage of the ROS generated for antibacterial impact, while low-to-moderate amounts of  $\text{H}_2\text{O}_2$  have antimicrobial and signaling effects (may assist reduce bacterial load and initiate repair pathways). But too much ROS can harm tissue, thus device design needs to take this into account.(14)





**Fig.3 Enzymatic Biofuel Cells.**

**Application:**

**Self-powered System:** EBFCs eliminate the need for external power sources by producing energy directly from endogenous biofuels like lactate and glucose in wound exudates.

**Biocompatibility:** To reduce tissue irritation, carbon-based electrode materials and enzymes can be made to be both biocompatible and biodegradable.

**Localized Electric Stimulation:** Constant low-level electrical output speeds up wound healing by encouraging angiogenesis, cell migration, and antimicrobial activity.

**Integration Potential:** EBFCs can be combined with drug-release systems, sensors, or smart dressings to provide multipurpose wound care.

**Eco-friendly Operation:** The system supports sustainability by using renewable biological fuels and operating under mild physiological settings.

**Limitation:**

**Enzyme Instability:** Enzymes in EBFCs, like glucose oxidase and laccase, are affected by temperature, pH, and breakdown by proteolytic enzymes, which decreases their stability and lifespan in body conditions.

**Limited Power Output:** The bioelectricity produced is usually in the microwatt range, which is not enough for the long-term or large-scale electrostimulation needed for healing chronic wounds.



**Substrate Dependence:**EBFCs depend on physiological substrates such as glucose and oxygen, which vary in concentration within wound tissues, causing inconsistent power output.

**Oxygen Limitation:**The lack of oxygen in the wound environment, particularly in chronic wounds, hinders cathodic reactions, leading to lower energy conversion efficiency.

**Biocompatibility and Toxicity Issues:**Certain mediators and electrode materials, like metal nanoparticles and conductive polymers, can lead to cytotoxic effects or inflammation in wound tissue.

**Mechanical and Integration Challenges:**It is technically challenging to maintain flexibility, adhesion, and proper contact with uneven wound surfaces while preventing irritation to the tissue

### **Piezoelectric nanogenerators (PENGs) :**

Piezoelectric nanogenerators (PENGs) are innovative self-powered devices that transform mechanical movements like body motions, breathing, or slight skin deformation into electrical signals. The small electric currents they produce replicate the body's own endogenous electric fields, which play a crucial role in speeding up the wound-healing process. The electromechanical interaction is known as piezoelectricity, which includes two types of effects the direct piezoelectric effect and the inverse piezoelectric effect. Piezoelectric materials consist of both natural and synthetic substances. Natural examples include crystals like quartz, Rochelle salt, topaz, and minerals from the tourmaline group, as well as organic materials such as silk, wood, enamel, bone, hair, rubber, and dentin. The direct piezoelectric effect occurs when a material generates an electrical output in response to mechanical stress; this electrical output is directly proportional to the amount of mechanical stress applied. Conversely, the inverse piezoelectric effect happens when a piezoelectric material undergoes mechanical deformation as a result of an applied electric field (EF). [15]

### **Mechanism:**

#### **Improved cell movement and growth:**

Electric stimulation from PENGs enhances the movement of fibroblasts and keratinocytes towards the wound area (galvanotaxis). Fibroblasts subjected to an electric field (~100 mV/mm) exhibit about a 100% rise in collagen production and a 20% increase in DNA production.

#### **Regulation of growth factors, ECM, and blood vessel formation:**

Electrical stimulation increases important healing factors such as TGF- $\beta$ , VEGF, FGF-2, and IGF-1. There are improved collagen deposition (notably type III to type I), better granulation tissue, enhanced re-epithelialization, and increased angiogenesis.

#### **Modulating the immune system & controlling inflammation**

Electrical fields can affect the type of macrophages (shifting from M1 to M2), lessen excessive inflammation, and encourage a more healing environment. A piezoelectric electrospun membrane that modulates the immune system has been shown to enhance macrophage activity, aiding in difficult wound healing.

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**Application:**

**Electrical Stimulation with Self-Power:** PENGs transform mechanical energy from bodily motion—such as breathing, heartbeat, or skin deformation—into electrical signals. These electrical impulses accelerate wound healing by stimulating cell migration, proliferation, and differentiation.

**Improvement of Angiogenesis:** By activating vascular endothelial cells, the electric field produced by PENGs promotes the development of new blood vessels and enhances the transport of nutrients and oxygen to the wound site.

**Effects of Antibacterials:** By rupturing bacterial cell membranes, the constant electrical output can lower the likelihood of infection at the wound site.

**Control of Cellular Functions:** PENGs affect collagen deposition, keratinocyte proliferation, and fibroblast alignment—all essential steps for successful tissue regeneration.

**Smart Wound Dressings:** PENGs can be included into biocompatible, flexible wound dressings to deliver electrical signals continually without the need for external power sources.

**Monitoring Healing in Real Time:** Certain sophisticated PENG systems have the ability to detect pressure or motion at the same time, allowing for both stimulation and healing progress monitoring.

**Limitation:**

**Low output performance:** For deeper or chronic wounds, the electrical output of contemporary PENGs is frequently insufficient to provide reliable therapeutic stimulation.

**Problems with material biocompatibility:** The biomedical applications of certain piezoelectric materials, such as lead zirconate titanate (PZT), are restricted due to their toxicity or lack of biodegradability.

**Mechanical durability:** Under repetitive deformation, flexible PENGs may experience mechanical fatigue or delamination, which lowers their long-term effectiveness.

**Moisture sensitivity:** The performance and stability of PENGs, particularly those composed of organic or hybrid materials, may be impacted by the humid wound environment.

**Limited clinical translation:** Large-scale human trials and regulatory approvals are absent, and the majority of research is still in the in vitro or animal model stage.

**Triboelectric nanogenerator (TENG):**

Triboelectric nanogenerators (TENGs) are a viable option to address the pressing need to combine thermal and electrical stimulation into a practical treatment strategy that may be used in everyday situations. More significantly, because of its special advantages such as a variety of operating modes, high energy conversion rates, and simple scalability TENGs may be able to provide on-site electrical stimulation to successfully accelerate skin wound healing. According to Ayurveda, an imbalance in three crucial aspects of the wrist pulse indicates a person's health and shows signs of illness. The design, sensing methods, performance, advantages, and disadvantages of various TENG-based blood pressure sensors are examined.[17]

An attractive method for treating Infected skin wounds is the use of wearable triboelectric nanogenerators (TENGs) as tiny electrical stimulation (ES) devices at the wound site. Nevertheless, it is still difficult to build an integrated TENG patch that achieves both regulated drug loading and release and in situ ES. In order to speed up the healing of infected wounds, a flexible TENG patch is logically constructed with a surface-engineered electrode that contains Mg-Al layered double hydroxide as a smart medicine container and friction layer. The surface-engineered TENG patch demonstrates efficient minocycline delivery and enhanced triboelectricity generation performance. According to in vitro findings, these TENG patches significantly increase fibroblast migration and proliferation while killing nearly 100% of E. coli and S. aureus.[18]



**Mechanism:**

**a) Cell migration and proliferation.:**

The localized electric field generated by PENGs induces galvanotaxis (or directed migration) in keratinocytes and fibroblasts, thereby enhancing their proliferation — which accelerates re-epithelialization and matrix formation.

**b) Modulation of ion channels and calcium signaling**

ES modifies membrane potentials and activates voltage-sensitive ion channels, particularly calcium channels, which function as second messengers to initiate proliferation, migration, and the release of growth factors.

**c) The facilitation of angiogenesis:**

which refers to the formation of new blood vessels, is influenced by electrical signals that enhance the expression of angiogenic factors such as VEGF and stimulate endothelial cell function. This process leads to improved blood flow to the wound site and aids in the development of granulation tissue. Such effects are frequently documented in in-vivo research involving piezoelectric dressings.

**d) Diminished inflammation and expedited remodeling:**

Several studies conducted on animals indicate that electrical stimulation (ES) from piezoelectric membranes decreases inflammatory markers, enhances collagen deposition, and accelerates the transition from the inflammatory phase to the proliferative/remodeling phases.[19]

**Application:**

Electrical Stimulation Therapy – Triboelectric Nanogenerators (TENGs) produce low-frequency electric fields that facilitate cell proliferation, migration, angiogenesis, and collagen synthesis, thereby expediting tissue regeneration.

Self-powered Wound Dressings – Flexible, wearable dressings based on TENG technology harness energy from body movements to provide continuous healing stimulation without the need for external power sources.

Antibacterial and Anti-inflammatory Effects – The application of electrical stimulation diminishes bacterial proliferation and regulates macrophage function, thereby promoting enhanced wound healing.

Controlled Drug Delivery – TENGs are capable of initiating the on-demand release of therapeutic substances, including antibiotics and growth factors.

Smart Wound Monitoring – Built-in sensors enable the real-time assessment of wound characteristics such as pH levels, temperature, and moisture content

**Limitation:**

Irregular Energy Source: Because TENGs rely on mechanical motion, patients who are immobile may have unstable energy output due to irregular body movement.

Low and Variable Power Density: For deep or chronic wounds that need long-term treatment, the electrical output ( $\mu\text{W}$ – $\text{mW}$  range) might not be enough.

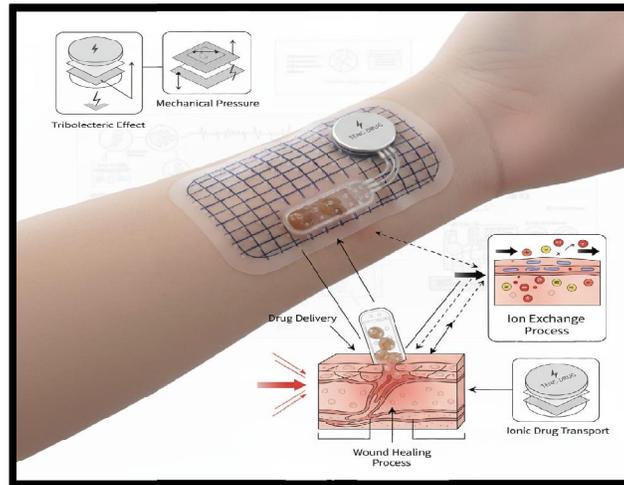
Material Durability: Triboelectric layers' lifespan may be shortened by frequent mechanical contact and exposure to the environment.

Biocompatibility Issues: If TENGs' synthetic polymers or surface coatings are improperly enclosed, they may trigger allergic or inflammatory reactions.

Integration Challenges: It is still technically challenging to maintain flexibility, breathability, and adherence to moist wound surfaces while guaranteeing comfort and electrical contact.

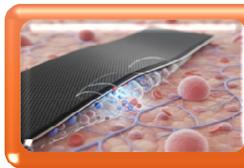
calability and Fabrication Costs: The development of flexible, wearable, and clinically safe TENGs on a large scale is still in its early stage.





**Fig.4 Wearable Triboelectric Nanogenerator Patch**

**Electrodes:**

	<p><b>carbon rubber electrodes:</b></p> <ul style="list-style-type: none"> <li>• Commonly use for indirect stimulation with saline-soaked gauze.</li> <li>• Durable, reusable, good conductivity.</li> </ul>
	<p><b>Metal plate electrodes:</b></p> <ul style="list-style-type: none"> <li>• Used in indirect setups or for large wound cares.</li> <li>• High conductivity and uniform current distribution.</li> </ul>
	<p><b>Hydrogel electrodes:</b></p> <ul style="list-style-type: none"> <li>• Used for direct wound contact conforms to wound surface.</li> <li>• Non-irritating, maintains moisture, flexible.</li> </ul>
	<p><b>Disposable adhesive electrodes:</b></p> <ul style="list-style-type: none"> <li>• Used in intact skin around the wound.</li> <li>• Convenient, hygienic, single use.</li> </ul>
	<p><b>saline-soaked gauze electrodes:</b></p> <ul style="list-style-type: none"> <li>• Commonly used as interface for periwound ES.</li> <li>• Easy, inexpensive, promotes moist healing.</li> </ul>

**Table.2 Types of Electrodes**



### **Types of Electric Stimulation Modalities:**

#### **Conducting polymers:**

Conductive polymers accelerate wound repair through electrical, biological, and material-based mechanism. Delivering the active ingredients to the intended location without harming healthy cells is one of the most sought-after aspects of the medication delivery system. Chemical or electrochemical oxidation can be used to create CPs; the latter method is frequently chosen because it produces polymeric films that are deposited on the anode surface and can be removed to produce free-standing films. Additionally, reactions in electrochemical synthesis can be conducted at room temperature. Electric charge generated by physiological reactions can be effectively transferred to electronic circuits by CPs. Additionally, CPs can be applied to specific electrode regions. The creation of amperometric biosensors has made extensive use of this special quality as well as the potential to trap enzymes during electrochemical polymerization.[20]

#### **Electroconductive hydrogels:**

Electroconductive hydrogels (ECHs) represent an advanced class of wound dressings that combine biocompatible hydrogel matrices with electrically conductive components such as polypyrrole, graphene derivatives, MXenes, or metallic nanoparticles. By re-establishing or augmenting the endogenous electrical gradients disrupted during tissue injury, these systems facilitate coordinated healing responses. ECHs promote wound repair by directing cell migration through galvanotaxis, enhancing cellular proliferation, stimulating neovascularization, and exerting intrinsic antimicrobial effects. Their hydrated, compliant structure enables intimate integration with wound beds while supporting controlled delivery of electrical cues, either via external power sources or self-generating mechanisms based on piezoelectric or triboelectric materials. Although ECHs demonstrate substantial potential for managing chronic wounds—including diabetic ulcers, burns, and infected lesions further work is required to optimize their biocompatibility, mechanical robustness, durability, and manufacturability to advance their clinical translation.[21]

#### **Microneedle patches:**

Micro needles have been used extensively in the treatment of numerous skin conditions as an appealing transdermal drug delivery method that is both painless and effective. The integration of microneedles with electric fields to construct electrical microneedles is the focus due to the potential to establish transdermal channels.

Microneedle patches featuring micro-nanostructures facilitate precise therapeutic drug delivery to living tissues, thereby achieving optimal therapeutic outcomes. The wound healing phase necessitates careful management to promote an improved healing condition, primarily due to the fact that the healing process is affected by numerous factors such as environmental conditions, age, nutritional status, and pharmacological treatments. [22]

Microneedling works by creating controlled micro-injuries in the skin using tiny needles, triggering a healing response that leads to skin rejuvenation. This process releases growth factors like PDGF, TGF- $\alpha$ , and TGF- $\beta$ , which promote neovascularization (new blood vessel formation) and neocollagenesis (new collagen production), improving skin texture and tightening it for years, especially through the formation of collagen type III.

An alternative theory suggests that the needles don't actually create wounds but instead alter the membrane potential of skin cells, tricking them into perceiving an injury. This stimulates the release of proteins and growth factors, which then encourage fibroblast migration and collagen synthesis.[23]

### **Types:**

#### **Conductive-Driven Microneedles**

Microneedles with electrically conductive fillers, such as conductive polymers, metals, carbon, MXene, etc., make up conductive-driven microneedles. The performance of microneedles, including their physical and chemical characteristics, electrical effects, and biological functions, can be readily adjusted for a variety of applications due to their flexible adjustability in terms of the conductive fillers, dopants, and cross-linking state. We'll give a quick overview of these conductive-driven microneedles.[24]



**Triboelectric-Driven Microneedles:**

A type of natural phenomena known as triboelectricity has the ability to transform mechanical actions into electrical signals without the need for external power sources. Contact electrification and electrostatic induction work in concert to provide this unique characteristic. Many triboelectric-driven devices have been proposed, and triboelectric nanogenerators (TEENG) are one of the most widely used energy collection technologies. These devices profit from the principle and their properties, which include self-powered ability, low cost, portability, implantability, and mild electrical stimulating conditions. Due to the more practical application of electrical stimulation into deeper tissue through the penetration of microneedle tips, which exhibits greater advantages over many conventional electrical therapy materials, triboelectric-driven microneedles are becoming more and more common.[25]

**Piezoelectric-Driven Microneedles:**

A piezoelectric-driven microneedle (PDMN) platform that achieves high efficiency, safety, and non-invasiveness is suggested. By creating deep tissue cavitation, this platform raises protoporphyrin IX levels and greatly improves medication penetration. A piezoelectric material is utilized to generate an acoustic field, achieving low-density and safe acoustic cavitation, and a specially designed microneedle array (MA) patch with multimicrochannels fabricated using a high-precision three-dimensional (3D) printing technology achieves skin-acoustic coupling and drug delivery.[26]

**MXenes-integrated microneedle:**

In biology, MXenes are new 2D nanosheets mainly used in combined chemotherapy for cancer treatment, bioimaging, and highly sensitive detection. They have outstanding mechanical properties and can load drugs at a remarkable rate of over 200%. Furthermore, MXenes are highly biocompatible and do not show any toxicity to normal cell lines. MXenes greatly enhanced the mechanical strength of microneedles, and  $\gamma$ -PGA hydrogels created a moist environment for healing wounds. Mice treated with MN-MXenes-AS showed clear improvements in the wound healing process. We successfully created a microneedle integrated with MXenes that has enough rigidity to penetrate the skin for delivering drugs under the skin, thus speeding up the healing of diabetic wounds. We showed that MN-MXenes-AS is effective in promoting growth both in living organisms and in laboratory settings.[27]

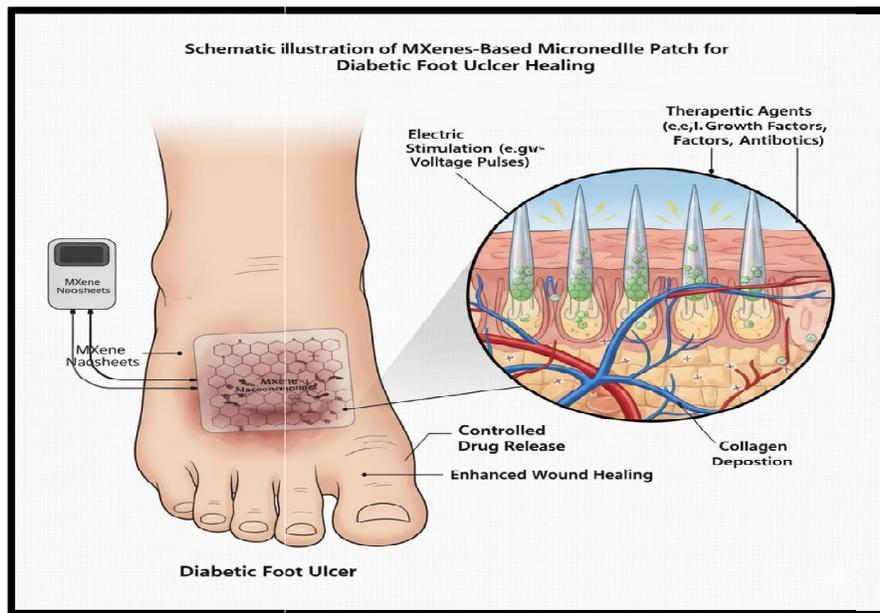


Fig.5 Schematic illustration of MXenes-based microneedle patch.



**Electroporation:**

Electroporation is an electrotherapeutic approach that applies short, high-voltage electrical pulses to transiently increase the permeability of cellular membranes. These pulses induce nanoscale pores within the lipid bilayer, enabling the intracellular transport of molecules that ordinarily cannot cross the membrane, including nucleic acids, proteins, peptides, antibiotics, and growth factors. By directly enhancing the uptake of therapeutic agents into resident skin cells, fibroblasts, endothelial cells, and immune cells within the wound microenvironment, electroporation provides a powerful means of overcoming the barriers that typically inhibit healing. One of the primary applications of electroporation in wound care is enhanced drug delivery. The technique facilitates the localized transport of antibiotics, anti-inflammatory drugs, metal ions, and antimicrobial peptides into deep wound tissues and biofilm-infected regions. In addition to drug delivery, electroporation has emerged as an important platform for non-viral gene therapy. Gene electrotransfer using plasmid DNA encoding regeneration-associated molecules such as VEGF, PDGF, HGF can stimulate angiogenesis, modulate inflammatory pathways, promote fibroblast proliferation, and improve overall tissue remodelling. [28]

**Iontophoresis:**

Iontophoresis is a non-invasive electrotherapeutic modality that employs low-intensity direct or pulsed electrical currents to enhance the transdermal and trans-wound transport of ionizable therapeutic agents. Through the combined mechanisms of electrorepulsion and electroosmosis, this technique substantially improves the delivery of antibiotics, anti-inflammatory compounds, metal ions, and growth factors into chronically impaired or poorly perfused tissues.[29] Beyond facilitating drug penetration, the applied electrical field contributes to wound repair by attenuating inflammatory responses, promoting fibroblast migration and collagen synthesis, stimulating angiogenesis, and exerting antimicrobial effects. Iontophoresis demonstrates considerable potential for the management of chronic wounds including diabetic ulcers, pressure ulcers, venous ulcers, and burns although its clinical application remains limited by factors such as shallow penetration depth, localized irritation, and the requirement for drugs with sufficient ionic charge.[30]

**Wounds healed by ES:**

**Pressure ulcers:**

Pressure ulcers (also known as pressure sores, decubitus ulcers or bedsores) are localised injuries to the skin or underlying tissue, or both. Pressure ulcers are a disabling consequence of immobility. Electrical stimulation (ES) is widely used for the treatment of pressure ulcers. Electrical stimulation (ES) is administered through an electrical current that can be applied to the skin using various methods. The application of ES necessitates the placement of a minimum of two small electrodes on the skin, which are linked to a compact battery-operated device that regulates the current's intensity. ES can be provided in the form of either a direct current or a pulsed current.[31]

**Hypertrophic scars:**

This phenomenon can be explained by the presence of a locally thickened dermis and dense collagen fibers in the scar tissue, which restricts the diffusion of the drug and hinders its ability to sustain a high concentration at the site of injection.(26) Researchers have created MNs containing triamcinolone acetonide, protocatechuic aldehyde, and betamethasone to reduce scars with less pain in vivo. Additionally, antineoplastic drugs have been applied to scar treatment. 5-Fluorouracil-loaded MNs decreased the levels of collagen I and transforming growth factor 1 $\beta$  (TGF-1 $\beta$ ), which led to less collagen fibre buildup and abnormal fibroblast growth. Dissolving HA-MNs with bleomycin also reduced the growth of hypertrophic scar fibroblasts and the release of TGF-1 $\beta$ . [32]



**Scleroderma-related ulcers:**

Research indicates that iontophoresis of the drug treprostinil can enhance wound healing in a mouse model of scleroderma-related ulcers. It is believed to enhance blood circulation by regulating the sympathetic nervous system, which results in vasodilation and improved oxygen supply to the impacted tissues.

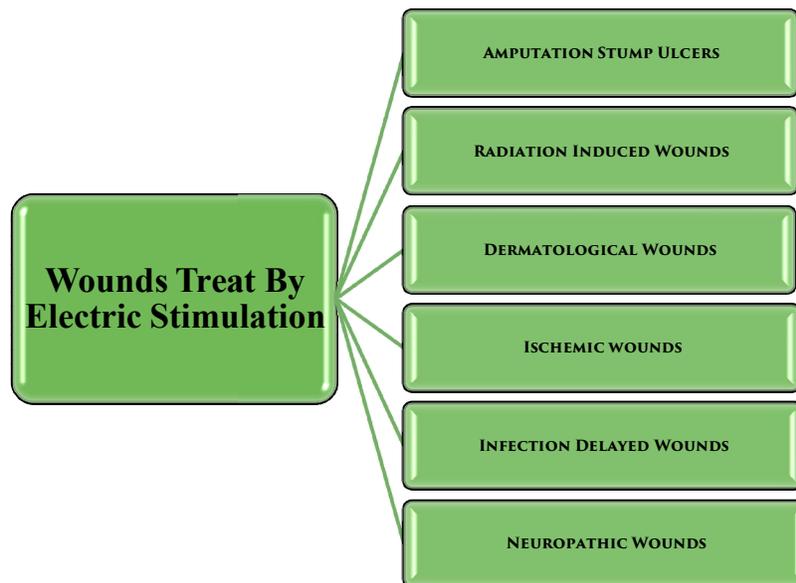
**Diabetic foot ulcers:**

Electrical stimulation enhanced the movement of diabetic fibroblasts, their ability to contract collagen gel, and the expression of alpha-smooth muscle actin, while also promoting various proteolytic enzymes that play a role in expediting wound healing. Low levels of electrical stimulation were able to activate skin fibroblasts obtained from diabetic patients.

Moreover, the stimulated cells exhibited enhanced proliferation and adequate migration following wound scratching, as well as increased contraction of collagen gel through the expression of  $\alpha$ -SMA protein. Additionally, the electrical stimulation facilitated the secretion of various matrix metalloproteinases (MMPs) recognized for their role in promoting wound healing. Overall, our findings indicate that electrical stimulation may serve as a promising approach for the treatment of chronic wounds, including diabetic foot ulcers.[33]

**Surgical and traumatic wounds:**

Electrical stimulation effectively enhances healing of surgical and traumatic wounds by promoting cell migration, angiogenesis, and tissue regeneration while minimizing infection and scarring. It serves as a safe, non-invasive, and evidence-based adjunct to conventional wound care.



**Fig.6 Wounds Treat By ES**

**Challenges:**

- The present kind, strength, duration, and waveform of ES are not standardized.
- There are few high-quality studies and few long-term clinical trials.
- Patient compliance and usability are negatively impacted by bulky, inflexible, or complicated devices.
- The potential for burns, skin irritation, and pH imbalance at electrode–tissue contacts.
- Conductive materials' instability in wet, enzymatic wound settings.



The inconsistent wound microenvironment makes it difficult to sustain consistent ES.  
Self-powered systems' limited lifespan and power output (PENGs, TENGs, EBFCs).  
ES is frequently insufficient on its own to completely penetrate or destroy established biofilms.  
Advanced conductive materials are expensive to produce and have limited scalability.  
Regulatory obstacles to the approval of combination or ES-based devices.  
Individualized ES techniques are complicated by patient-to-patient variability.[34]

#### **Future Prospects:**

Creation of intelligent ES dressings that can automatically modify electrical parameters and monitor them in real time.  
The incorporation of self-powered systems, either physiologically or mechanically, to provide continuous stimulation and remove reliance on batteries.  
The development of multifunctional electroconductive biomaterials that combine tissue-regenerative, antibacterial, and antioxidant properties with conductivity.  
Enhanced combination therapies, in which ES facilitates gene transfer, growth factor release, or tailored medication administration for better healing.[35]  
Better methods for managing biofilms and infection, employing ES as a synergistic antibacterial mechanism.  
ES-based platforms that support deep tissue repair through angiogenesis, nerve regeneration, and stem cell activation.  
The creation of closed-loop, adaptive ES systems that react to mechanical or biochemical changes in wounds.  
Dosage, frequency, and electrode design standardization to facilitate robust clinical translation and regulatory approval.[36]

### **III. CONCLUSION**

Electrical stimulation demonstrates substantial therapeutic value in the management of chronic and non-healing wounds by reinstating physiological electric fields and promoting key regenerative events such as galvanotaxis, neovascularization, and extracellular matrix synthesis. The development of innovative self-powered systems most notably piezoelectric and triboelectric nanogenerators, enzymatic biofuel cells, and conductive biomaterials has broadened the applicability of ES, enabling continuous and targeted stimulation within the wound microenvironment. Although the current evidence strongly supports the clinical promise of ES-based technologies, further optimization of stimulation parameters, long-term biocompatibility, and large-scale clinical validation remain essential for successful translation into routine wound care. Collectively, ES integrated with advanced biomaterials represents a forward-looking strategy capable of significantly improving therapeutic outcomes in chronic wound treatment.

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