



A self-powered Zn—Mo hydrogel battery patch for synergistic electrochemical wound healing

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ABSTRACT

Current smart wound dressings that integrate wound monitoring and electrical stimulation primarily rely on flexible electronic systems composed of multiple sensors and external power sources. However, their clinical translation is significantly hampered by unstable energy output and high interfacial impedance between the bioelectronic device and biological tissues, which together disrupt stable, long-term interactions with cells and impair therapeutic efficacy. Herein, we present a novel electrochemical strategy based on a minimalist, self-powered wound patch that unifies stimulation generation and delivery within a single integrated platform. The system employs a Zn—Mo hydrogel-based battery (E-PGA) to autonomously provide sustained low-voltage direct current while simultaneously releasing bioactive zinc ions, thereby synergistically modulating the wound microenvironment. This dual-mode action potently enhances fibroblast functions—including proliferation, migration, and growth factor secretion—and drives macrophage polarization toward a pro-regenerative phenotype through suppression of pro-inflammatory cytokines (e.g., TNF- α , IL-1 β). In vivo studies demonstrate accelerated and robust wound closure with improved tissue regeneration. By eliminating the need for external power and minimizing interfacial complexity, this approach offers a scalable, biocompatible, and clinically translatable paradigm for next-generation electroactive wound care. Moreover, it provides a versatile platform to investigate the fundamental mechanisms by which electrical cues regulate cellular behavior during tissue repair.

1. Introduction

The skin is the largest organ of the human body, accounting for approximately 10% of total body weight and performing a wide array of essential physiological functions. It serves as a protective barrier against harmful chemicals, ultraviolet radiation, and pathogenic microorganisms; synthesizes vitamin D; regulates body temperature; and prevents excessive water loss [1]. Structurally, the skin comprises three interconnected layers—epidermis, dermis, and subcutaneous tissue—arranged from superficial to deep [2]. Disruption of its normal architecture and function by physical, chemical, or biological insults can lead to wound formation. The wound healing process typically progresses through four overlapping phases: hemostasis (coagulation), inflammation, proliferation, and remodeling [3]. Systemic or local factors may perturb the wound microenvironment, thereby impairing the

repair cascade and potentially resulting in delayed healing or chronic, non-healing wounds. Conventional wound management strategies—including debridement, antimicrobial dressings, hyperbaric oxygen therapy, and negative pressure wound therapy—often fail to directly modulate the activity of endogenous cells at the wound site, limiting their efficacy and the rate of tissue regeneration. With advancing insights into the molecular and cellular mechanisms of wound repair, therapeutic emphasis has shifted from passive interventions such as debridement and topical coverage toward more sophisticated, microenvironment-targeted approaches for chronic wound treatment.

In recent years, electrical stimulation has gained increasing attention as an active intervention in physical therapy for wound healing. This approach is rooted in the pioneering observation by German physiologist Emil Du Bois-Reymond, who first documented the presence of

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endogenous electrical currents in wounds [4]. These bioelectric signals originate from ion channels, ion pumps, and electrically coupled intercellular junctions in cell membranes and play a pivotal role in coordinating cellular behaviors during tissue repair. Subsequent work by Ghadamali et al. demonstrated that the strength of endogenous electric fields (EFs) in acute skin wounds correlates positively with wound surface area [5]. Accumulating evidence indicates that such EFs effectively regulate the proliferation and migration of keratinocytes, fibroblasts, and endothelial cells, thereby accelerating re-epithelialization, collagen deposition, and angiogenesis [6].

Building on this physiological foundation, electrical stimulation therapy exerts its effects by mimicking or amplifying the naturally occurring electric fields at the wound site through externally applied currents [7]. Application of electrical stimulation around the wound not only alleviates edema but also enhances the recruitment of chemotactic immune cells and guides cellular proliferation, migration, and differentiation. Notably, macrophages, lymphocytes, and neutrophils have all been shown to undergo directional migration toward the wound under the influence of endogenous EFs [8]. Furthermore, Seren et al. reported that transcutaneous electrical nerve stimulation (TENS) significantly suppresses the expression of pro-inflammatory cytokines in the skin—including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β)—thereby mitigating inflammation and shortening the overall healing timeline [9]. Collectively, these findings underscore the multifaceted mechanisms by which electrical stimulation modulates the wound microenvironment and highlight its considerable potential for clinical translation in regenerative wound care.

The rapid progress in flexible electronics has paved the way for self-powered, wearable electrical stimulation patches, offering a promising alternative for chronic wound management. Among available energy sources, biobatteries stand out due to their high energy density, excellent electrochemical stability, and inherent biocompatibility with human tissues—minimizing immunogenic risk while ensuring consistent power output over extended periods. These attributes render biobatteries particularly well-suited for powering long-term therapeutic devices in wound care. Consequently, bio-battery-driven electrical stimulation patches represent a compelling strategy to overcome existing limitations in chronic wound therapy, enabling more effective and user-friendly treatment modalities. A prevailing design paradigm involves the integration of self-powered modules directly into medical dressings to create autonomous electronic skin systems [10–12]. In this context, metal-based microbatteries have attracted considerable interest owing to their capacity to generate sustained electrical stimulation through spontaneous electrochemical reactions without the need for external power or control circuitry. Notably, biodegradable metals such as magnesium (Mg) and zinc (Zn) have been widely adopted in the development of microbattery-integrated dressings [13,14].

Glycyrrhizic acid (GA), a naturally occurring triterpenoid saponin, exhibits a wide range of pharmacological properties, such as antioxidant, anti-inflammatory, antibacterial, and antiviral activities. Despite these beneficial effects, its clinical utility is constrained by factors including limited aqueous solubility, low oral bioavailability, cytotoxicity at elevated doses, and pronounced hemolytic activity. Consequently, the integration of glycyrrhizic acid into a hydrogel matrix to create a hydrogel dressing with improved anti-inflammatory capabilities represents a promising strategy for enhancing wound healing outcomes. Herein, we report the development of *E*-PGA, a fully biodegradable, self-powered bioelectronic patch that seamlessly integrates low-voltage electrical stimulation with intrinsic anti-inflammatory therapy. The system operates autonomously without external power sources or auxiliary equipment, delivering stable low-voltage direct current (LVDC) throughout the healing process while eliminating thermal injury risks associated with high-voltage inputs [15]. Crucially, the entire architecture is physiologically resorbable: the poly-L-lactic acid (PLLA) nanofiber scaffold hydrolyzes into lactic acid, the gelatin methacryloyl (GelMA) hydrogel matrix enzymatically degrades into amino acids and

peptides, and the zinc (Zn)/molybdenum (Mo) electrochemical couple corrodes into biocompatible byproducts, thereby obviating the need for secondary removal procedures [16,17].

The fabrication process of the *E*-PGA bioelectronic patch is schematically illustrated in Fig. 1. The patch features a concentric architecture engineered to recapitulate the spatial orientation of endogenous electric fields in wounds. The base layer consists of an electrospun PLLA nanofiber membrane, which provides mechanical support and prolongs functional durability. Embedded within the core is a GelMA-based hydrogel matrix containing GA, which houses concentric Zn and Mo electrodes; this configuration generates an exogenous electric field aligned with the natural wound field while delivering sustained LVDC stimulation. Furthermore, the inherent anti-inflammatory properties of glycyrrhizic acid provide significant anti-inflammatory efficacy to the dressing. Comprehensive *in vitro* assessments were performed to evaluate biocompatibility, fibroblast migration, angiogenic potential, and expression levels of key markers—including type I collagen (Col I), CD31, and α -smooth muscle actin (α -SMA)—alongside *in vivo* studies using a full-thickness skin injury model [18]. The results demonstrate that the *E*-PGA dressing, by emulating endogenous electric field dynamics, significantly enhances fibroblast migration, collagen deposition, and neovascularization, culminating in accelerated wound closure. Collectively, these findings highlight the substantial translational potential of this bioelectronic patch for the treatment of chronic wounds.

2. Results and discussions

2.1. Characterization of the *E*-PGA bioelectronic patch

Photocurable methacrylated gelatin was prepared as Fig. 2a. Under UV light, the photoinitiator generates free radicals that react with the double bonds of the photosensitive methacrylamide groups on GelMA, introducing free radicals onto GelMA [19]. Subsequently, free radical migration occurs, attacking the free methacrylamide double bonds upstream of GelMA until the copolymerization reaction terminates, ultimately forming crosslinked molecular chains. Subsequently, nano-sized zinc particles and molybdenum particles were incorporated into the prepared gelatin methacrylate to fabricate concentric-circular hydrogel zinc batteries (Fig. 2a). FTIR spectra show that the gelatin amide I band at 3305 cm^{-1} ; Amide I band at 1629 cm^{-1} primarily originates from C=O stretching vibrations; Amide II band at 1539 cm^{-1} results from combined C—N stretching and N—H bending vibrations. The Amide III band at 1240 cm^{-1} is primarily attributed to CH₂ rocking vibrations, N—H bending vibrations, and C—N stretching vibrations. The peak shapes of the GelMA precursor and gelatin are highly similar, with the Amide II band slightly shifted toward higher frequencies [20]. This shift results from the introduction of methacrylamide groups onto the gelatin molecular chains, confirming the successful preparation of methacrylated gelatin (Fig. 2b). The surface morphology of the *E*-PGA patch was observed by scanning electron microscopy (SEM) (Fig. 2c). We found that the PLLA fibers exhibit relatively good orientation, making them suitable as substrates for hydrogel zinc batteries. It revealed that the UV-crosslinked GelMA hydrogel scaffolds exhibited porous, sponge-like, loose structures with uniform pore sizes.

2.2. Mechanical properties of *E*-PGA

For an ideal wound dressing, appropriate flexibility and elasticity are crucial to mitigate mechanical complications and prolong service life [21]. Accordingly, the mechanical properties of *E*-PGA were systematically evaluated. In the 0–10% strain range, tensile stress increased linearly and rapidly, indicating excellent elastic recovery of the PLLA fiber membrane. This behavior enables the dressing to provide responsive elastic support during minor skin deformations, significantly mitigating the risk of immediate rupture upon stretching [22]. Beyond 10% strain, the stress–strain curve exhibited a plateau followed by a peak and

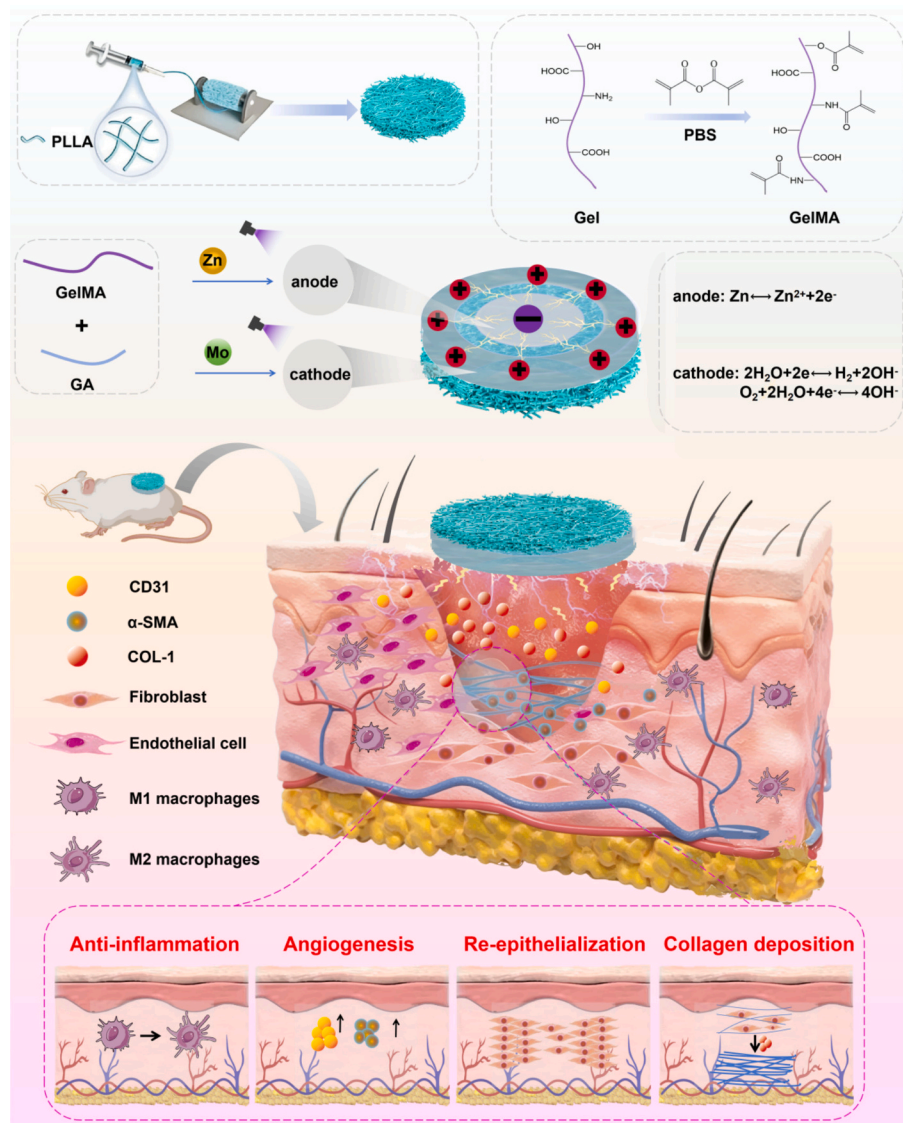


Fig. 1. Schematic diagram of E-PGA dressing preparation and wound healing promotion mechanism.

a gradual decline, characteristic of a transition to plastic deformation. This ductile response allows the material to accommodate significant movements at dynamic wound sites (e.g., joints), thereby preventing catastrophic failure under excessive deformation. Notably, the PLLA backing achieved a fracture strain of approximately 35%, demonstrating high elongation at break and sufficient flexibility to meet the mechanical demands of daily activities while maintaining structural integrity. The mechanical performance of the hydrogel-based anodes and cathodes was also evaluated. Across all groups, compressive stress increased nonlinearly with strain, with no fracture plateau observed even at strains up to 70%. This confirms the exceptional compressive toughness and deformation resistance of the GelMA-based hydrogel, which effectively prevents fragmentation under load while maintaining structural integrity. At low strains (0–30%), the gradual stress increase highlights the hydrogel's inherent flexibility and elastic recovery, allowing it to conform seamlessly to soft tissues without causing mechanical mismatch. Conversely, at higher strains (30–70%), stress rose sharply, indicating pronounced strain-hardening behavior. This adaptive stiffening ensures that under significant compression, the hydrogel provides robust mechanical support to limit excessive tissue deformation and mitigate potential damage (Fig. 2d–e). The incorporation of nano-zinc and nano-molybdenum significantly enhanced compressive strength,

with nano-zinc demonstrating a superior reinforcing effect compared to nano-molybdenum (Fig. 2f). This suggests that metal nanoparticles improve crosslinking density and network stability, thereby boosting compressive resistance. While the pure GelMA system exhibited the lowest mechanical performance, the addition of GA improved its properties, and the combination of GA with metal nanoparticles—particularly nano-zinc—yielded the optimal mechanical characteristics. These results indicate that co-crosslinking interactions between GA and GelMA, synergized with metal nanoparticles, facilitate the formation of a denser three-dimensional network with superior mechanical properties.

2.3. In vitro swelling, degradation and drug release behaviors of the hydrogels

The swelling and degradation properties of hydrogels are critical factors for applications such as wound dressings and drug delivery systems, as they influence the release of active components within the hydrogel. Therefore, hydrogels were immersed in PBS solution to evaluate their swelling performance. As shown in the Fig. 2g, the swelling rates of all experimental groups exhibited a rapid upward trend, with the fastest swelling occurring within the first 5 h. This occurs because

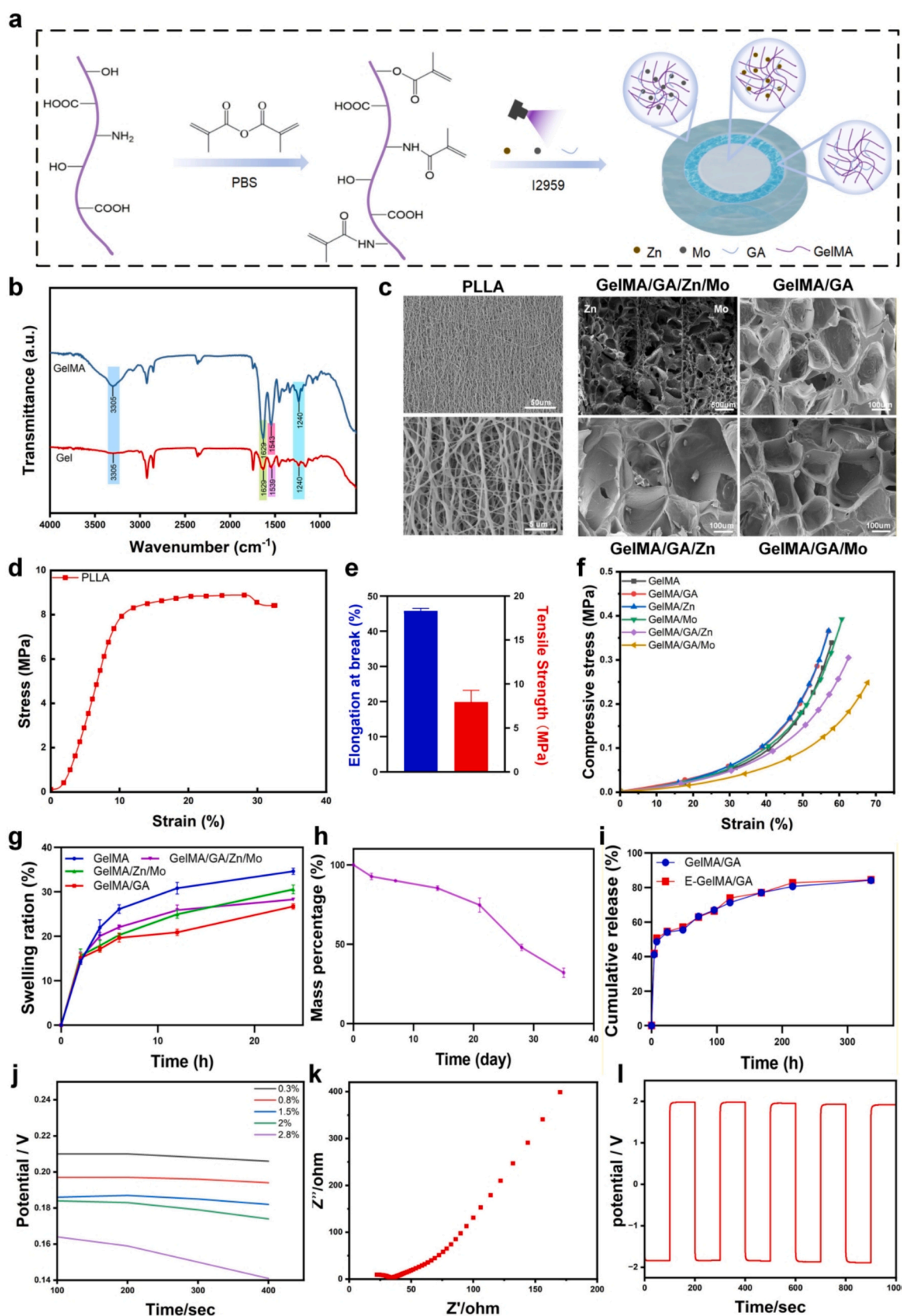


Fig. 2. Characterization and Electrical and electrochemical properties of E-PGA membranes. a) The preparation process of Zn–Mo Hydrogel-based Battery. b) FTIR of Gel and GelMA. c) SEM images of PLLA films and hydrogels. d) Tensile curves, e) elastic modulus and toughness of PLLA films. f) Compression curves of hydrogels. g) Swelling curve of hydrogel. h) Degradation curve of E-PGA. i) Cumulative release profile of GA from E-PGA at pH 7.4. j) Open circuit voltage (V_{oc}) of the E-PGA membranes. k) AC impedance of E-PGA. l) Constant current charge-discharge curve of E-PGA.

hydrophilic groups within the hydrogel network (e.g., amide groups, carboxyl groups) rapidly bind with water molecules, allowing water to penetrate the gel interior swiftly. This demonstrates the excellent hydrophilicity and rapid water absorption of this hydrogel. After 10 h, the swelling rate significantly slowed, and the curve gradually flattened, indicating that the hydrogel network approached a swollen equilibrium state. Its three-dimensional crosslinked structure restricted further water molecule penetration, demonstrating swelling stability. The swelling rate of pure GelMA was significantly higher than that of the GelMA/GA group, indicating that the introduction of GA increases the crosslinking density of the hydrogel, reduces network porosity, and consequently decreases water molecule penetration, leading to a lower swelling rate. In the GelMA/GA system, the introduction of Zn/Mo resulted in a slight recovery of the swelling rate. Similarly, Zn/Mo incorporation into the pure GelMA system (GelMA/Zn/Mo) resulted in a swelling rate slightly lower than pure GelMA but higher than GelMA/GA. This may be due to the metal ions doping moderately regulates the network pore structure of the hydrogel, preserving a certain amount of hydrophilic space while ensuring crosslinking stability, positioning the swelling rate between pure GelMA and GelMA/GA. A degradation study of *E*-PGA was conducted in phosphate-buffered saline (PBS). As shown in Fig. 2h, the degradation process progressed slowly during the initial phase, with the structural integrity preserved. By approximately day 35, the zinc-molybdenum hydrogel-based battery had completely degraded, leaving only the PLLA fiber membrane intact.

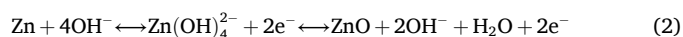
We investigated the release profile of GA from *E*-PGA hydrogels. As shown in the Fig. 2i, the curve exhibits a rapid upward trend from 0 to 100 h, with a cumulative release rate of approximately 70% within the first 100 h. This rapid release is attributed to the swift dissolution of glycyrrhizic acid from the gel surface and superficial layers, coupled with water absorption-induced swelling that expands the surface network pores. This accelerates initial drug release, demonstrating rapid-onset drug delivery characteristics that facilitate the transition of wounds from the inflammatory phase to the proliferative phase [23]. Between 100 and 300 h, the release rate decelerated significantly, with the curve approaching a plateau. By 300 h, the cumulative release reached approximately 85%, without reaching complete release. This profile indicates that GA is released via a combination of diffusion and hydrogel network degradation, demonstrating robust sustained-release capabilities. Such a mechanism helps maintain therapeutic drug concentrations at the wound site, thereby minimizing the need for frequent dressing changes. Notably, the incorporation of nano-zinc and nano-molybdenum did not significantly alter the GA release kinetics.

2.4. Electrical and electrochemical properties

The discharge performance of Zn—Mo hydrogel-based battery was tested using physiological saline as the electrolyte. The reaction occurring at the anode is expected to be the oxidation of zinc [24]:



Additionally, side reactions may occur when zinc reacts directly with the electrolyte, resulting in an increase in pH near the anode. Byproducts such as zinc hydroxide or zinc oxide (ZnO) may form, coating the surface of the zinc electrode [25]. These substances gradually dissolve in aqueous environments, such as physiological saline [26].



At the cathode, either hydrogen evolution (Eq. (3)) or oxygen reduction (Eq. (4)) may occur [27,28]:



Using an electrochemical workstation, the open-circuit voltage

stability over time was tested for electronic patches doped with varying concentrations of nano-zinc and nano-molybdenum. This evaluation assessed the patches' ability to maintain potential under no-load conditions. Results indicate that lower concentrations (e.g., 0.3%) yield higher initial open-circuit voltages (approximately 0.21 V), while higher concentrations (e.g., 2.8%) produce lower initial voltages (approximately 0.16 V) (Fig. 2j).

This phenomenon arises from the balance between ionic conductivity and structural stability within the hydrogel. At low concentrations, the hydrogel network is looser, resulting in lower ionic transport resistance and a higher initial potential. Conversely, at high concentrations, nanoparticle filling increases the network density, which raises ionic transport resistance and lowers the initial potential. Additionally, the patch with a 2.8% concentration exhibited the fastest voltage decay, dropping from 160 mV to 140 mV within 400 s. In contrast, the patch with a 0.8% concentration maintained a relatively stable voltage of approximately 190–200 mV, demonstrating superior open-circuit voltage stability. Therefore, the patch containing 0.8% zinc/molybdenum nanoparticles was selected for subsequent studies. Testing the AC impedance of the patches (Fig. 2k) revealed low resistance and low interfacial impedance, facilitating effective electrical stimulation. This indicates that the ion concentration and mobility within the hydrogel are at optimal levels. Zinc ions can be rapidly conducted, providing a stable current foundation for the external electric field. The calculated conductivity (0.051 S cm^{-1}) indicates moderate conductivity, ensuring the device delivers a stable and gentle external electric field that avoids skin irritation or tissue damage caused by current fluctuations. The moderate diffusion rate of zinc ions maintains a dynamic equilibrium of local zinc ion concentration at the wound site, preventing cellular toxicity from excessive zinc levels. Additionally, zinc ions possess inherent antibacterial properties that help reduce the risk of wound infection [29]. Constant-current charge-discharge testing of the electronic patch produced characteristic “square wave” charge-discharge curves (Fig. 2l), reflecting the electrochemical stability and practical suitability of the battery for wound treatment.

2.5. Effect of Zn—Mo hydrogel-based battery on cell migration and proliferation

Cellular compatibility is a fundamental requirement for bio-electronic patches intended for use as advanced wound dressings. To evaluate the biocompatibility of the fabricated electronic patches, human skin fibroblasts (HSFs)—central mediators of wound healing processes including re-epithelialization, collagen deposition, and extracellular matrix remodeling—were exposed to patch extracts, and their responses were assessed using CCK-8 and live/dead fluorescence assays [30]. Following 24 h of co-culture with the extract, HSFs exhibited viability comparable to that of the control group, with no significant induction of apoptosis and maintenance of a healthy, spindle-shaped morphology characteristic of active fibroblasts (Fig. 3a). Over an extended culture period, both experimental and control groups showed progressive increases in cell numbers, reflecting normal proliferative behavior. Notably, the *E*-PGA group demonstrated a significantly enhanced proliferation rate throughout the three-day incubation period. These findings were corroborated by CCK-8 assay results, which collectively confirm the excellent cytocompatibility of the bioelectronic patch and its intrinsic ability to actively promote HSF proliferation (Fig. 3b). Given that the capacity to stimulate cell migration is a critical determinant of a material's efficacy in accelerating wound closure, a standard scratch assay was employed to evaluate this functional attribute. As illustrated in Fig. 3c, HSFs treated with the *E*-PGA patch displayed markedly accelerated migration into the wounded area compared to all other tested groups. Quantitative image analysis at the 12-hour timepoint revealed that the *E*-PGA group achieved over 91% wound coverage, substantially outperforming the control (41.58%), PG (57%), PGA (69.7%), and *E*-PG (75.8%) groups (Fig. 3d). This superior

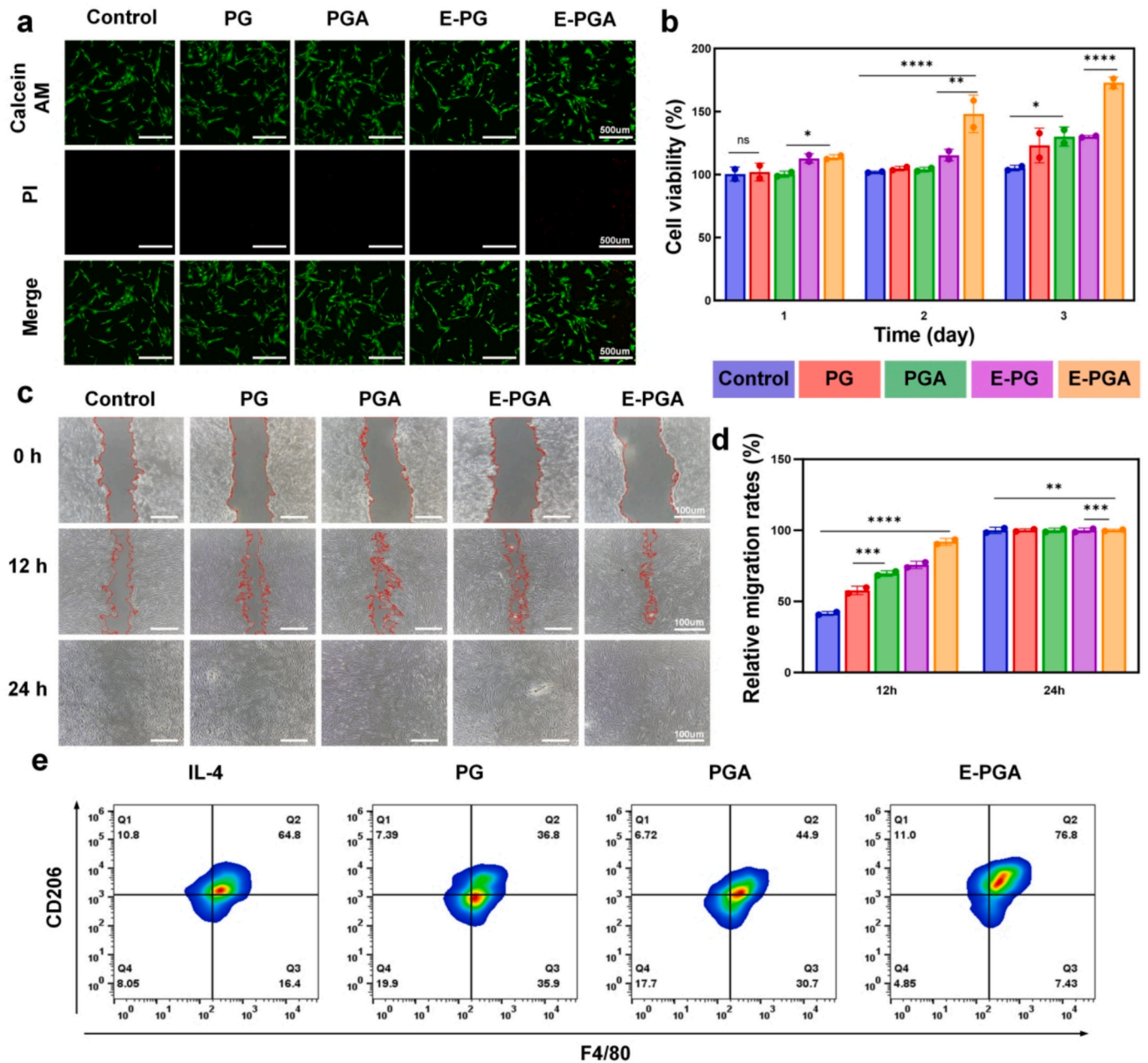


Fig. 3. The effects of the E-PGA membranes on fibroblast migration and Macrophage. a) Live/dead fluorescent staining images of HSF cells cultured on the E-PGP membranes after 24 h. b) Relative viability of HSF cells cultured on the E-PGA membranes after 1, 2, and 3 days. c) Scratching images of HSF cells treated by the PGP and E-PGP membranes with 0, 12, and 24 h. d) Quantitative analysis of scratch healing in HSF cells under different treatments. e) Flow cytometry analysis of macrophage transition toward M2 phenotype. All data are plotted as means $\pm$ SD ($n = 3$), $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$.

migratory response is attributed to the electrical stimulation delivered by the integrated Zn—Mo hydrogel-based battery in the E-PGA system, which effectively mimics endogenous electric fields known to guide directional cell movement during physiological wound healing [31]. The results demonstrate that the E-PGA bioelectronic patch not only supports cellular viability but also actively enhances key regenerative processes—proliferation and migration—thereby offering a promising strategy for electrically assisted wound repair.

2.6. Effect of Zn—Mo hydrogel-based battery on regulating inflammatory response

Successful wound re-epithelialization hinges on the dynamic progression from the inflammatory to the proliferative phase, a transition

critically regulated by macrophages [32]. While M1 macrophages mediate host defense via pro-inflammatory cytokine secretion—potentially exacerbating tissue damage if prolonged—M2 macrophages secrete anti-inflammatory factors that actively facilitate tissue repair. To investigate the impact of electrochemical stimulation on macrophage polarization, we analyzed the expression of the M2 marker CD206 using flow cytometry. RAW 264.7 cells were first primed toward the M2 phenotype with interleukin-4 (IL-4) for 24 h, followed by co-culture with the bio-patches for an additional 24 h. Post-stimulation, macrophages in the E-PGA group adopted a characteristic short spindle morphology with prominent membrane protrusions, indicative of an M2 phenotype (Fig. S1, Supporting Information). Quantitative flow cytometry (Fig. 3e) confirmed a significant upregulation of CD206 in the E-PGA group (76.8%), substantially surpassing the PGA (44.9%) and PG

(36.8%) groups. These findings demonstrate that bioelectrochemical stimulation effectively drives macrophage polarization toward the reparative M2 phenotype. This strategy offers a promising therapeutic avenue for modulating inflammatory responses in chronic wounds and burn injuries.

2.7. Accelerated wound healing using the Zn—Mo hydrogel-based battery

We employed the developed bioelectronic patch to treat full-thickness circular excisional wounds (10 mm in diameter) created on the dorsal skin of rats, aiming to evaluate its *in vivo* wound-healing efficacy. The treatment protocols and representative macroscopic images captured throughout the healing course are summarized in Fig. 4a–c, with quantitative assessment of wound closure rates provided in Fig. 4d. By day 7 post-wounding, the electrically stimulated groups—E-PG and E-PGA—exhibited markedly accelerated healing, achieving wound closure rates of 90.15% and 90.99%, respectively. In contrast, the control, PG, and PGA groups showed significantly slower progression, with healing rates of only 60.35%, 70.77%, and 86.40%, respectively. By day 14, although most wounds across all groups had largely re-epithelialized, the electrically stimulated groups displayed more complete and uniform tissue coverage, whereas the non-stimulated groups—including the control—continued to exhibit delayed closure and less mature granulation tissue. Notably, the final wound healing rate in the control group reached 89.38%, while the E-PGA group—which integrates both electrical stimulation and glycyrrhizic acid (GA)—achieved the highest efficacy at 97.12%, outperforming the PG (94.34%),

PGA (94.41%), and E-PG (95.01%) groups. This enhanced therapeutic outcome aligns well with our *in vitro* observations, reinforcing the functional synergy between electrostimulation and bioactive GA delivery. Collectively, these findings demonstrate that the bioelectronic patch significantly accelerates cutaneous wound repair *in vivo*. The superior performance is likely attributable to the synergistic interplay between electrical stimulation—which promotes fibroblast proliferation and directional migration by mimicking endogenous bioelectric cues—and the anti-inflammatory activity of GA, which modulates the local immune microenvironment to favor tissue regeneration [33,34].

To comprehensively evaluate the *in vivo* wound-healing efficacy of the bio-patches, histological analyses of regenerated skin tissue were conducted at days 3, 7, and 14 post-treatment using hematoxylin–eosin (H&E) and Masson's trichrome staining (Fig. 5a–b). Granulation tissue formation and re-epithelialization serve as critical hallmarks of cutaneous repair. H&E staining revealed that at day 3, the control group exhibited pronounced inflammatory cell infiltration within the wound bed, accompanied by delayed epithelial migration. In contrast, the PG and PGA groups displayed reduced inflammation and early signs of epithelial advancement toward the wound center. Notably, the electrically stimulated E-PG and E-PGA groups demonstrated markedly attenuated inflammation and significantly accelerated re-epithelialization. By day 14, the E-PGA group achieved superior tissue maturation, characterized by well-developed fibroblasts and emerging hair follicles, outperforming all other groups. Quantitative analysis of epidermal thickness (Fig. 5c) confirmed that the E-PGA group exhibited a substantially thicker epidermis (75.64 μm) compared to the control

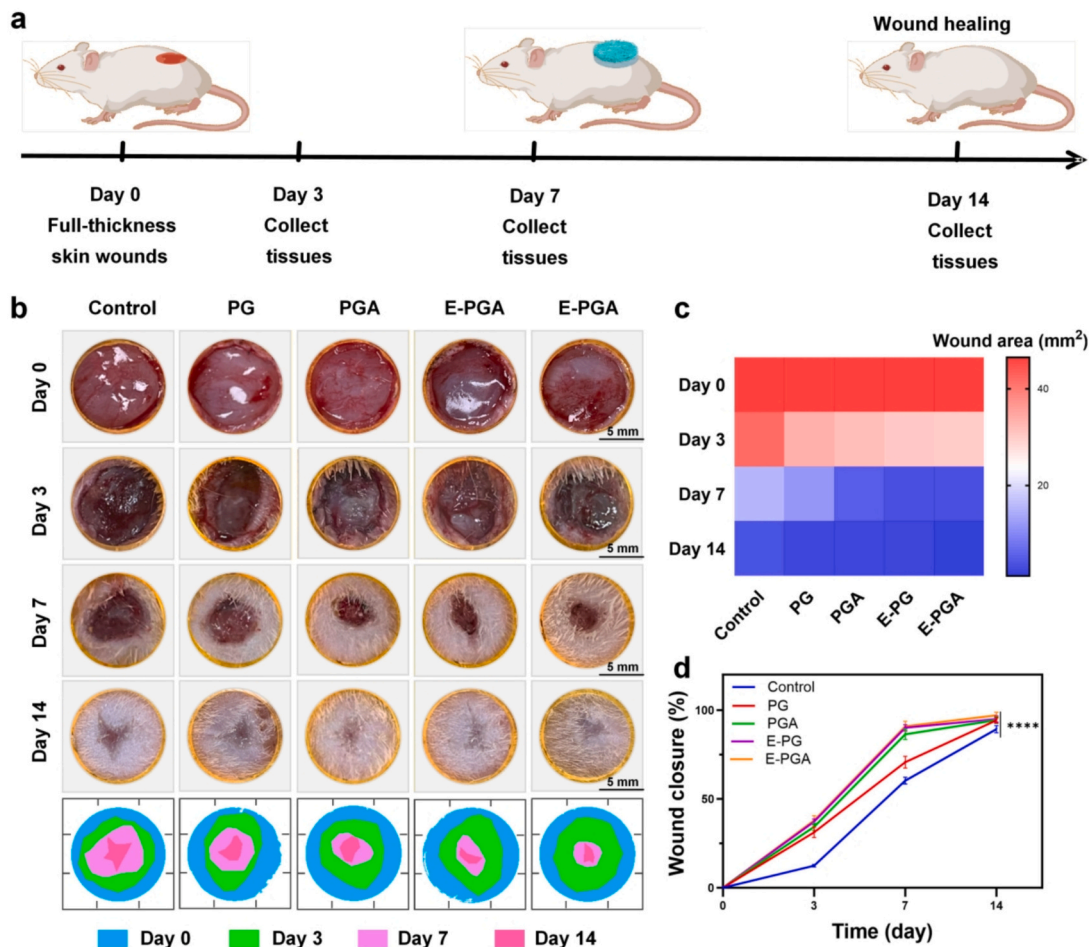


Fig. 4. *In vivo* wound closure assessment. a) Schematic and timeline for the full-thickness wound treatment process. b) Representative images, c) comparable representation, and d), e) quantitative analysis of the wound healing process in different groups. All data are plotted as means $\pm$ SD ($n = 3$), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

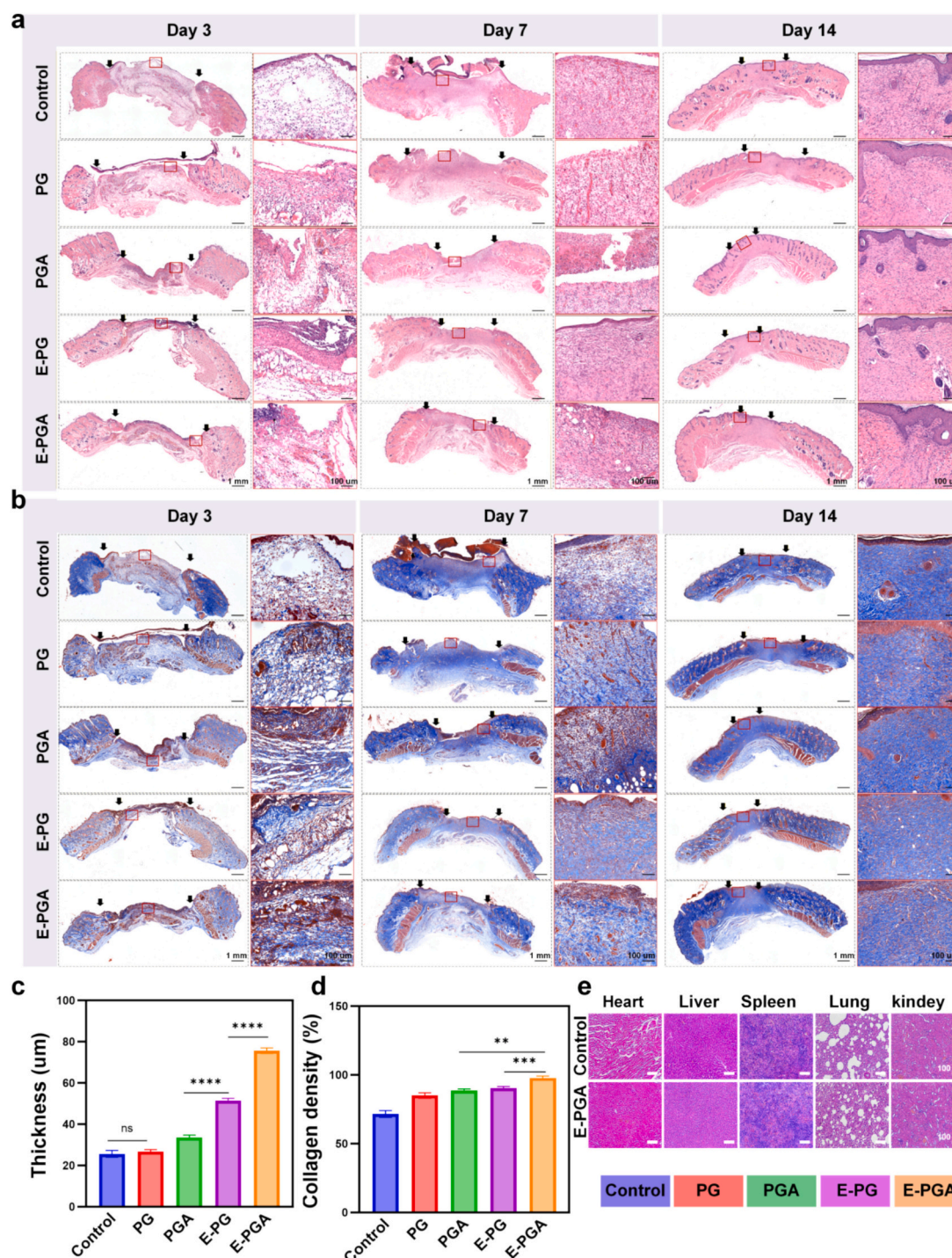


Fig. 5. Histological analysis of the in vivo application of E-PGA. a) H&E and b) Masson staining images of wound tissues on days 3, 7, and 14. c) Quantitative epidermal thickness, d) collagen density. e) Hematoxylin and eosin (H&E) staining of various visceral organs harvested from intestinal wound rats model 14 days after E-PGA treatment. All data are plotted as means as $\pm$ SD ($n = 3$), $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$.

(25.66 μm), PG (26.77 μm), PGA (33.54 μm), and E-PG (51.47 μm) groups, underscoring its enhanced regenerative capacity. Collagen deposition, a pivotal parameter in dermal reconstruction, was assessed via Masson's trichrome staining (Fig. 5b). Throughout the healing process, the E-PG and E-PGA groups exhibited denser and more extensive collagen fiber networks, whereas the control, PG, and PGA groups showed relatively sparse and disorganized deposition. By day 14, collagen fibers in the electrically stimulated groups had matured into tightly packed, highly organized architectures. Quantification of the collagen volume fraction (Fig. 5d) revealed values of 90.45% and

97.85% for the E-PG and E-PGA groups, respectively, significantly surpassing those of the control (71.64%), PG (85.02%), and PGA (88.50%) groups. These findings suggest that while GA-loaded patches (PG/PGA) partially alleviate inflammation via sustained glycyrrhizic acid release, the integration of electrical stimulation in the E-PG and E-PGA systems confers a synergistic advantage—evidenced by robust suppression of early-phase inflammation and rapid epithelial migration. Collectively, these data indicate that the bioelectronic patches accelerate wound closure primarily by enhancing re-epithelialization and promoting high-fidelity collagen deposition.

To assess systemic biosafety, major organs (heart, liver, spleen, lung, and kidney) from treated rats were subjected to H&E histopathological examination. As shown in Fig. 5e, no discernible histological abnormalities or signs of tissue damage were observed in any organ after 14 days of treatment, confirming the excellent *in vivo* biocompatibility and safety profile of the developed bioelectronic patches.

To further elucidate the mechanism by which the prepared hydrogel modulates the wound healing process, immunohistochemical analysis was conducted to detect the expression of representative cytokines (Fig. 6a). As shown in Fig. 6a, collagen I expression levels gradually increased over time across all groups, exhibiting a trend consistent with the results of Masson's trichrome staining. On day 7, collagen I expression was higher in the E-PGA group compared to the other groups. By day 14, all groups exhibited elevated collagen I expression, consistent with the findings on day 7. Quantitative analysis (Fig. 6b) revealed collagen I expression levels of 83.84%, 84.02%, and 87.79% in the PGA, E-PG, and E-PGA groups, respectively—all significantly higher than those in the control group (64.46%) and the PG group (66.42%), indicating that the E-PGA bioelectronic patch possesses a distinct advantage in promoting collagen deposition. These findings further confirm E-PGA's capacity to facilitate wound remodeling. The nutritional supply to newly formed granulation tissue is closely linked to the formation of new blood vessels within the wound. Emerging capillaries deliver nutrients and oxygen to the wound site, supporting tissue regeneration. Thus, the characteristics of angiogenesis are crucial for wound healing. Positively stained endothelial cells (CD31) represent a vascular endothelial-specific marker expressed during early angiogenesis and are associated with neovascularization, while α -smooth muscle actin (α -SMA) serves as a marker for vascular smooth muscle cells involved in wound contraction and tissue repair [35]. In addition, by day 7, the PGA, E-PG, and E-PGA groups exhibited denser capillary distribution, with the E-PGA group demonstrating the highest expression of CD31 and α -SMA. In contrast, only sparse capillaries were observed in the control and PG groups. By day 14, capillary numbers remained relatively high in the control, PG, and PGA groups, while they significantly decreased in the E-PG and E-PGA groups. Quantitative analysis (Fig. 6c-d) revealed α -SMA and CD31 expression levels of 1.69% and 0.86% in the E-PGA group, substantially lower than those in the other groups. This vascular regression indicates that the wound has entered the vascular maturation phase [36]. These findings suggest that the E-PGA bioelectronic patch generates a higher-density vascular network during the early stages of wound healing, thereby promoting orderly vascular regression and accelerating tissue repair. According to Li et al. [37], electrical stimulation significantly enhances angiogenesis by upregulating CD31 expression, leading to increased capillary density. Thus, the E-PGA electronic patch demonstrates significant therapeutic effects across all stages of wound healing due to its self-powered electrical stimulation capability. Concurrent analysis of cytokine and growth factor levels in wound tissues at 3 and 14 days post-treatment is presented (Fig. 6e-h). Tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) are prototypical pro-inflammatory cytokines expressed during the early wound healing phase. Interleukin-10 (IL-10) serves as an anti-inflammatory cytokine marker for assessing wound repair efficacy, while transforming growth factor- β (TGF- β) indicates fibroblast proliferation and extracellular matrix production [38]. ELISA results (Fig. 6e-h) revealed that various pro-inflammatory factors (TNF- α , IL-1 β), primarily released by M1 macrophages, were downregulated in the electrostimulation group compared to other groups. Conversely, the anti-inflammatory cytokine IL-10 was significantly upregulated in the electrostimulation group. Upregulation of TGF- β expression was observed in the E-PGA-treated group. These findings further demonstrate that the E-PGA bio-patch serves as an excellent wound dressing capable of stimulating cell proliferation and migration, suppressing inflammation, and promoting angiogenesis. Moreover, accelerated wound healing may be attributed to the bio-battery's immunomodulatory capacity. Concurrently, electrochemical stimulation from the bio-battery facilitates the

transition from the early inflammatory phase to the proliferative phase, while enhancing angiogenesis and extracellular matrix deposition during the proliferative phase.

3. Conclusion

Conclusively, this study presents an innovative bioelectronic patch embedding flexible microbatteries to provide on-site electrical stimulation for accelerated wound repair. The device effectively drives fibroblast proliferation and migration while facilitating the M1-to-M2 macrophage polarization *in vitro*. In a 10 mm full-thickness wound model, the patch significantly hastened healing by promoting angiogenesis and modulating the immune response—specifically, by elevating anti-inflammatory and angiogenic factors while down-regulating TNF- α and IL-1 β . These findings validate the efficacy of integrating self-powered energy units into flexible biomedical devices. Recent studies have demonstrated that multifunctional hydrogel systems can effectively target pathological hallmarks through integrated therapeutic approaches. For example, Nayak et al. developed cell-laden hemostatic hydrogels capable of simultaneously modulating hemostasis, inflammation, and angiogenesis, thereby promoting comprehensive repair of diabetic wounds [39]. Inspired by these multifaceted strategies, we are currently designing follow-up studies to evaluate the efficacy of E-PGA in diabetic wound models, where the combined effects of electrical stimulation, zinc ion release, and glycyrrhizic acid-mediated anti-inflammatory activity are expected to enhance therapeutic outcomes. This strategy not only bridges the gap between energy storage and tissue engineering but also establishes a versatile platform for next-generation smart wound dressings with broad clinical potential.

4. Experimental section

4.1. Materials

PLLA (Mw 110,000) and Nano-molybdenum were purchased from Macklin. Hexafluoroisopropanol (HFIP) solution and Gel were purchased from Aladdin (China). GA was purchased from Shanghai Adamas Reagent Co Ltd. Methacrylic acid anhydride was purchased from Bide Pharmatech Ltd. Dulbecco's Modified Eagle Medium (DMEM), PBS, trypsin, Calcein-AM/PI double-labeled kit, and CCK-8 solution were purchased from Solarbio (China).

4.2. Preparation of PLLA nanofiber films

PLLA nanofiber films were prepared by electrospinning a 10% (w/v) PLLA/HFIP solution, which was stirred overnight for complete dissolution. The solution was electrospun using a 5 mL syringe at a feed rate of 1 mL/h under an electric field of +13 kV (needle) and −3 kV (collector). Other parameters included a collector speed of 1000 rpm, a working distance of 10 cm, and a spinning time of 1.5 h. The collected fibers were dried in a fume hood overnight to remove residual solvent. For SEM analysis, 2 mm × 2 mm fiber segments were mounted on conductive tape, sputter-coated with gold, and imaged to evaluate their microstructural morphology.

4.3. Synthesis of gelatin methacryloyl (GelMA)

GelMA precursor was synthesized by dissolving 10 g of gelatin in 100 mL of DI water at 60 °C, followed by the dropwise addition of methacrylic anhydride (0.8 mL/g gelatin, 1 mL/min). The reaction proceeded at 50 °C for 3 h, after which the mixture was diluted with 400 mL of warm DI water (50 °C). Following centrifugation (3000 rpm, 10 min), the supernatant was dialyzed against DI water at 50 °C for one week, frozen at −80 °C, and lyophilized [40]. The product was characterized by FT-IR spectroscopy.

For hydrogel preparation, the GelMA precursor was dissolved in an

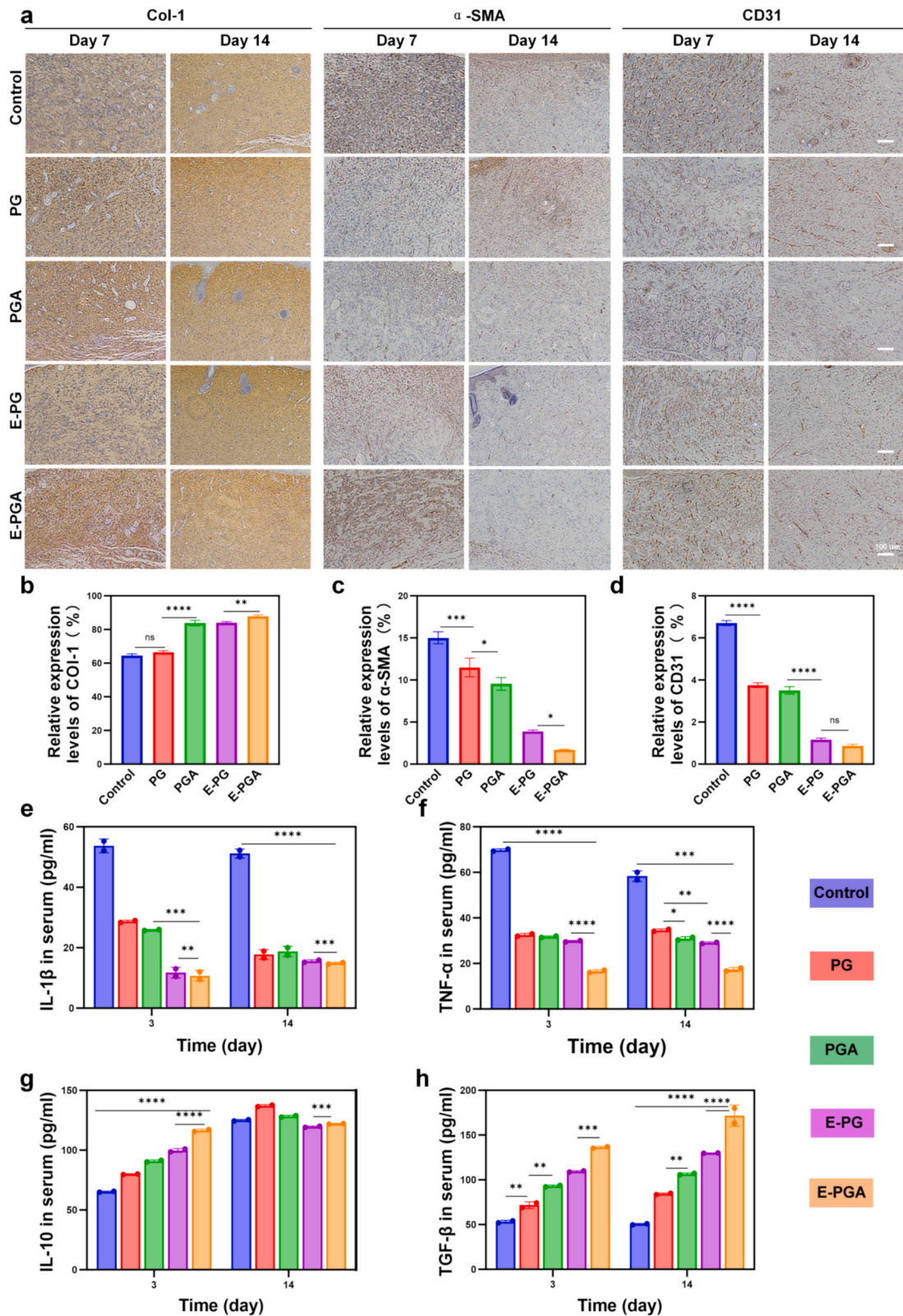


Fig. 6. In vivo collagen deposition and angiogenesis evaluation. a) Immunohistochemical staining of Col I, α -SMA and CD31 in wound tissue sections on the 7th day and 14th day. b) Quantitative analysis of Col I deposition. c) Quantitative analysis of α -SMA deposition. d) Quantitative analysis of CD31 deposition. e) IL-1 β , f) TNF- α , g) IL-10 and h) TGF- β expression level in the wound tissue on 3 and 14 days under different treatments. All data are plotted as means $\pm$ SD ($n = 3$), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

aqueous solution containing 0.5% Irgacure 2959 and photo-crosslinked via UV irradiation (1 min) to form 18% (w/w) hydrogels. Microstructural analysis was performed using SEM. Samples were freeze-dried, cryo-fractured in liquid nitrogen to reveal cross-sections, sputter-coated with gold, and imaged to evaluate their morphology.

4.4. Preparation of wearable bioelectronic patch

An 18 wt% GelMA precursor solution was prepared by dissolving GelMA in phosphate-buffered saline (PBS, pH 7.4). To formulate composite solutions, predetermined amounts of gallic acid (GA) were dissolved in the PBS prior to GelMA addition, yielding a GelMA/GA solution. Subsequently, nano-zinc (nano-Zn) powder was dispersed into both the pristine GelMA and GelMA/GA solutions to obtain GelMA/Zn and GelMA/GA/Zn suspensions, respectively. Similarly, nano-molybdenum (nano-Mo) powder was incorporated into the base solutions to prepare GelMA/Mo and GelMA/GA/Mo suspensions.

The wearable bioelectronic patch was fabricated via a sequential injection and photopolymerization strategy on a PLLA fibrous membrane. First, the Zn-containing hydrogel precursor was injected to form a central circular region with a diameter of 7 mm. Following this, the Mo-containing precursor was injected to form a concentric outer ring, resulting in a final construct with a total diameter of 1 cm. After 1 min of UV irradiation, the multi-layered structure was crosslinked, consisting of a central Zn electrode, an intermediate GelMA electrolyte layer, and an outer Mo electrode (from inner to outer). The detailed compositions of the various patch formulations are summarized in Table S1.

4.5. Mechanical characterization

PLLA Nanofiber Membranes: The mechanical properties of the electrospun PLLA nanofiber membranes were evaluated via uniaxial tensile testing at room temperature using a universal testing machine. Rectangular specimens (approx. 60 mm × 10 mm) were cut from the fiber mats, and their thickness was precisely measured using a micrometer prior to testing. The tensile tests were conducted at a constant crosshead speed of 5 mm/min. Each sample was tested in triplicate ($n = 3$), and the results are reported as the mean values.

GelMA Hydrogels: For compressive testing, cylindrical hydrogel specimens with dimensions of 20 mm in diameter and 12 mm in height were prepared. Compression tests were performed on a universal testing machine at a constant displacement rate of 5 mm/min until the desired strain was reached. All measurements were conducted in triplicate to ensure reproducibility.

4.6. Electrical and electrochemical properties

The open-circuit voltage (OCV) and galvanostatic charge-discharge (GCD) profiles of the samples were evaluated using an electrochemical workstation. Ionic conductivity was determined via electrochemical impedance spectroscopy (EIS) using a CHI660e workstation over a frequency range of 1 Hz to 1 MHz. The ionic conductivity (σ) was calculated according to the following equation:

$$\sigma = \frac{1}{R} \frac{d}{A}$$

where σ denotes the ionic conductivity ($S \cdot m^{-1}$), R (Ω) is the resistance obtained from the high-frequency intercept on the real axis of the AC impedance plot, and d and A correspond to the thickness and cross-sectional area of the material, respectively.

4.7. In vitro swelling, degradation and drug release behaviors

The swelling kinetics of the hydrogels were evaluated using a gravimetric method. Disc-shaped samples (15 mm diameter, 2 mm

thickness) were prepared, and their initial dry weights were recorded as W_d . The samples were then immersed in phosphate-buffered saline (PBS, pH 7.4) at 37 °C to simulate physiological conditions. At predetermined time intervals, the samples were removed, gently blotted with filter paper to remove surface water, and weighed to obtain the swollen weight (W_s). This process was repeated until swelling equilibrium was reached. The degree of swelling (DS, %) was calculated using the following equation:

$$\text{Swelling degree (\%)} = (W_s - W_d) / W_d \times 100\%$$

The biodegradation profile of the hydrogels was assessed by monitoring mass loss in PBS at 37 °C over time. At specific intervals, samples were retrieved, freeze-dried, and weighed to determine the remaining dry weight (W_t). The degradation rate was calculated based on the initial dry weight (W_d) and the remaining dry weight (W_t) using the following formula: Degradation rate (%) = $(W_d - W_t) / W_d \times 100\%$ [41].

To evaluate the effectiveness of GA in simulating drug release in body fluids, the hydrogel containing GA was enclosed in a dialysis bag and immersed in 100 mL of simulated body fluid. The setup was then shaken at a constant temperature of 37 °C and a rotation speed of 110 rpm. At predetermined intervals, 1 mL of the solution was withdrawn to measure drug concentration, and an equal volume of buffer solution was added to maintain the total volume, allowing the GA release experiment to continue.

4.8. In vitro biocompatibility and cellular assays

Proliferation: Material extracts (PG, PGA, E-PG, E-PGA) were prepared by incubating 5 g of sterilized samples in 50 mL DMEM at 37 °C for 24 h. Human skin fibroblasts (HSFs, 5×10^4 cells/well) were cultured in 96-well plates with these extracts or control DMEM for 1–3 days. Viability was measured via CCK-8 assay after 2 h incubation with the reagent. Morphology was assessed by Live/Dead staining on day 1 using a Leica DM6000 microscope (Ex/Em: ~490/545 nm).

Migration: In a scratch assay, confluent HSF monolayers (5×10^5 cells/well) were scratched, washed, and co-cultured with materials for 24 h. Migration was imaged optically, and the wound closure ratio was quantified via ImageJ based on the change in scratch area.

Immune Regulation: RAW 264.7 macrophages (2×10^5 cells/well) were treated with IL-4 (20 ng/mL) to induce M2 polarization while co-culturing with PG, E-PG, or E-PGA for 24 h. CD206 expression levels were subsequently analyzed by flow cytometry.

4.9. In vivo animal studies

4.9.1. Ethical statement and animal preparation

Twelve male Sprague-Dawley (SD) rats (8 weeks old, 180–220 g) were purchased from the Animal Experiment Center of Shenyang Pharmaceutical University. All animals were housed under standard conditions with access to food and water ad libitum and underwent a 7-day acclimatization period prior to experimentation. This study was approved by the Animal Ethics Review Committee of Shenyang Pharmaceutical University (Approval No.: SYPU-IACUC-S2025-0716-211). All procedures strictly adhered to relevant ethical guidelines and institutional requirements for the care and use of laboratory animals. At the conclusion of the study, animals were euthanized humanely in accordance with established protocols.

4.9.2. Surgical procedure and wound model establishment

Rats were anesthetized via intraperitoneal injection of 20% urethane solution (7.5 mL/kg). Anesthesia depth was confirmed by the loss of the righting reflex before the animals were transferred to a sterile surgical field and secured in a prone position. The dorsal hair was removed using electric clippers, and the exposed skin was disinfected with povidone-iodine. Two circular full-thickness skin wounds (10 mm in diameter)

were created on the dorsum of each rat using a sterile biopsy punch. The excision extended through the dermis to the subcutaneous layer, ensuring no damage to the underlying fascia or muscle.

The rats were randomly divided into five groups ($n = 6$): four treatment groups (PG, PGA, E-PG, and E-PGA) and one untreated control group. The treatment groups received immediate coverage with the respective sterile materials, while the control group received no intervention. All wounds were covered with 3 M transparent film dressings to prevent displacement of the materials and protect against infection. Post-surgery, rats were returned to their cages and monitored until full recovery from anesthesia.

4.9.3. Wound healing assessment

Wound healing was documented via digital photography on days 0, 3, 7, and 14. The wound area was quantified using ImageJ software. The wound healing rate was calculated using the following formula:

$$\text{Wound healing ratio (\%)} = (A_0 - A_t) / A_0 \times 100\%$$

where A_0 represents the initial wound area on day 0, and A_t denotes the wound area at the specified time point.

4.9.4. Histopathological and immunohistochemical analysis

On day 14, rats were euthanized under deep anesthesia. Full-thickness skin samples, including the wound bed and surrounding healthy tissue, were excised, rinsed with physiological saline, and fixed in 4% paraformaldehyde at 4 °C for 24 h. Fixed tissues were processed for routine paraffin embedding and sectioned. Sections were stained with Hematoxylin and Eosin (H&E) for general morphological observation and Masson's trichrome for collagen deposition analysis.

Immunohistochemical (IHC) staining was performed to evaluate the expression of CD31, Type I Collagen (Col I), and α -smooth muscle actin (α -SMA, a marker for myofibroblasts). Stained sections were examined under a light microscope to assess re-epithelialization, granulation tissue formation, and collagen remodeling.

Additionally, wound tissues were homogenized to measure inflammatory cytokine levels via Enzyme-Linked Immunosorbent Assay (ELISA). The concentrations of M1-associated pro-inflammatory cytokines (TNF- α , IL-1 β) and M2-associated anti-inflammatory cytokines (TGF- β , IL-10) were quantified to evaluate the immunomodulatory effects of the treatments.

4.9.5. In vivo biocompatibility evaluation

To assess systemic biocompatibility, major organs (heart, liver, spleen, lungs, and kidneys) were harvested from both treated and control rats upon euthanasia. Tissues were fixed, paraffin-embedded, sectioned, and stained with H&E. Histopathological examinations were conducted to detect any signs of toxicity, inflammation, or abnormal tissue architecture.

4.10. Statistics and reproducibility

One-way analysis of variance (ANOVA) among multiple groups was performed for statistics. P values were calculated by GraphPad Prism Software (version 9). The data in the figures were marked by $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$. All the data were reported as the mean $\pm$ SD. No animals were excluded from the analysis. No data were excluded from the analyses.

CRediT authorship contribution statement

Weiting Wang: Writing – original draft, Investigation. **Linyu Mo:** Investigation, Data curation. **Qiuling Han:** Investigation. **Yumo Chang:** Investigation. **Zhou Li:** Resources, Project administration. **Zhaoxu Meng:** Writing – review & editing, Funding acquisition. **He Lian:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

There are no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijbiomac.2026.153305>.

Data availability

Data will be made available on request.

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