

RESEARCH ARTICLE OPEN ACCESS

AI-Guided 4D Printing of Carnivorous Plants-Inspired Microneedles for Accelerated Wound Healing

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Received: 14 December 2025 | **Revised:** 1 March 2026 | **Accepted:** 23 March 2026

Keywords: 4D printing | adhesive DNA | artificial intelligence | biomimicry | chronic wound healing

ABSTRACT

Artificial intelligence (AI) integrated with bioinspired design enables the development of materials that adapt and dynamically respond to biological cues. In this study, a *Drosera capensis*-inspired thermo-responsive microneedle (MN) platform was developed, integrating motion, surface, and functional mimicry through AI-guided 4D printing. Shape memory polymers (SMPs) composed of tert-butyl acrylate (tBA) and 1,6-hexanediol diacrylate (HDDA) were designed to exhibit reversible shape recovery upon thermal stimulation. The complex shape-memory behavior was quantitatively modeled using multiple machine learning (ML) algorithms, including support vector regression (SVR), extreme gradient boosting (XGB), and Gaussian process regression (GPR). Among them, GPR demonstrated superior predictive accuracy ($R^2 > 0.99$) and provided predictive means and 95% confidence intervals, highlighting its reliability in modeling nonlinear thermal recovery behavior and its potential for guiding process parameter optimization. The resulting MNs exhibited *Drosera capensis*-like coiling and grasping motions, enabling self-actuating wound closure. Furthermore, the MNs were functionalized with adhesive DNA (aDNA) and Zn nanolayers via sputtering-based plasma immersion ion implantation (S-PIII). The Zn nanolayers facilitated sustained DNA release and endowed the MNs with intrinsic antibacterial activity. In diabetic wound models, the AI-optimized biomimetic MN (BMMN) system significantly enhanced epithelial regeneration, collagen remodeling, and neovascularization, demonstrating adaptive and intelligent wound healing materials.

Hyun Lee and Moon-Jo Kim contributed equally to this work.

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1 | Introduction

Human creation has been greatly influenced by the long history of bioinspiration, the practice of taking inspiration from the designs and functions found in nature [1–3]. From early innovations such as bird-inspired human flight to more recent advances in material science and engineering, nature has continuously provided a model for resolving challenging issues. Motion mimicry, functional mimicry, and surface property mimicry are the three general manifestations of this technique [4–6]. Surface property mimicking focuses the reproduction specific surface characteristics found in nature [6]. Dragonfly and cicada wings show amazing antibacterial properties from nanopillared designs [7, 8]. When these surfaces come into contact, they mechanically rupture bacterial cell membranes, enabling antibacterial activity without relying on chemical agents. A lotus leaf's superhydrophobic surface has helped create coatings and self-cleaning materials that reject contaminants and water [9]. On the other hand, function mimicry entails replicating the mechanical or metabolic functions found in animals, including the imitation of natural components. The advancement of adhesives modeled after mussel foot proteins has resulted in the formulation of robust, waterproof adhesives for medical and industrial applications [10–13]. In a similar manner, imitating the biomineralization process of diatoms, a previous study has utilized DNA to mineralize biosilica, resulting in nanotherapeutics that improve wound healing [14]. These DNA-induced biosilica materials enhance reactive oxygen species scavenging, angiogenesis, and anti-inflammatory activities, thereby expediting the healing of acute and chronic wounds. By comprehending and mimicking these natural elements, researchers can create novel materials that provide improved functionality and performance. Motion mimicry replicates the dynamic movements and responsive behaviors of biological organisms. An exemplary case is the advancement of soft robotics modeled after the movement of octopuses and starfish, which possess no stiff skeletal frameworks [15–17]. These soft robots can move across complex and constrained environments by mimicking the fluid and adaptive movements of their biological counterparts. Another instance is the development of artificial muscles that emulate the quick movements of the Venus flytrap, enabling machines to execute swift and precise moves [18, 19]. By mimicking these natural movements, researchers can create systems that are more adaptable and efficient in many environments.

Building on the idea of motion mimicry, shape memory polymers (SMPs) offer a viable method for simulating the dynamic movements seen in nature [20, 21]. A family of smart materials known as SMPs has the ability to change from a permanent shape to a transient, distorted shape [22, 23]. The polymer is physically distorted into the required transient shape under specific conditions, such as heating above its glass transition temperature. The material retains its temporary structure until it is subjected to an external stimulus that causes it to return to its original shape. SMPs respond to a variety of stimuli, including changes in pH, exposure to light, electrical or magnetic fields, temperature fluctuations, and chemicals [24, 25]. In recent years, SMPs have garnered a lot of interest in biomedical research due to their potential for minimally invasive procedures [26, 27]. They can be easily inserted into the body and, in response to physiological conditions, grow to their functional permanent shape since they

can be programmed into a compact temporary shape [28–30]. This feature is particularly useful for developing tissue-engineered structures, self-deploying stents, and other medical devices that require precise shape changes in situ [31]. As manufacturing technology advances, the performance of SMPs has been greatly enhanced by using 4D printing, which combines 3D printing processes with the capacity to alter shape over time [32–34]. This novel method makes it possible to create dynamic systems that closely mimic natural motions, creating new opportunities in domains where controlled motion and transformation are crucial, such as soft robots, flexible materials, and biomedical devices.

The largest organ in the body, the skin is essential for fluid balance, thermoregulation, sensory perception, and protection from environmental threats [35]. When wounds are produced by trauma, burns, surgery, or chronic illnesses, the skin begins a complex healing process that involves phases of hemostasis, inflammation, proliferation, and remodeling [36–38]. Proper wound management is essential to restore the skin's functionality and integrity. Nonetheless, the body's typical healing process may be impeded by factors such as infection, insufficient wound closure, and diminished vascularization [39–41]. Effective wound closure is crucial for minimizing scar formation, expediting healing, and averting pathogen infiltration [42, 43]. Recent wound closure techniques, including sutures, staples, and adhesives, exhibit shortcomings, such as exacerbating tissue damage, creating potential entrance points for bacteria, and failing to maintain consistent tension across the wound [44]. Moreover, adhesives may lack enough biocompatibility or strength, and their efficacy may be diminished in humid conditions or on irregular wound surfaces [44–46]. Since antibiotic-resistant bacteria are becoming more common and making wound care more difficult, infection prevention is essential [47–49]. The majority of conventional antimicrobial treatments use topical or systemic antibiotics, which can lead to resistance and have short-term localized efficacy [50]. Additionally, materials that may be altered without impairing mobility are required for joint injuries or those with complex forms. Innovative wound care solutions that promote tissue regeneration, adapt to the shape and mobility of the wound, effectively close wounds, and have antibacterial properties to prevent infection must be developed. Incorporating SMPs and advanced fabrication techniques, such as 4D printing, into wound healing devices holds great potential.

Despite the promise of 4D printing, the printing outcomes are governed by a complex interaction of material composition, curing parameters, environmental temperature, and time-dependent behaviors. Identifying optimal printing and post-processing conditions through conventional trial-and-error approaches is both labor-intensive and time-consuming. To overcome these limitations, machine learning (ML) has recently been introduced as a data-driven approach to accelerate design, process optimization, and predictive control in 3D/4D printing systems. ML algorithms can efficiently learn nonlinear relationships between multiple experimental inputs and target outputs, thereby enabling predictive modeling across diverse bioprinting tasks [51, 52]. Beyond material formulation, ML has also been utilized to optimize extrusion parameters, printing speed, and curing time to improve structural fidelity and reproducibility in bioprinted constructs [53, 54]. Collectively, these studies highlight the growing role of ML as a bridge between experimental data and rational process design in

biofabrication. Nevertheless, current ML-bioprinting integrations remain largely focused on printability or morphological fidelity, while dynamic and shape recovery of printed structures have been rarely modeled. For functional biomaterials, capturing the coupled effects of curing conditions, material concentration, and external thermal environment is essential. A data-driven predictive framework capable of learning such complex dependencies could substantially reduce experimental workload and guide rational design of smart printing systems.

Motivated by the need to address the aforementioned challenges, we established a bioinspired design framework derived from the coordinated functional strategy of *Drosera capensis*. This carnivorous plant exhibits three biologically integrated features highly relevant to wound healing including stimulus-responsive motion for prey capture, adhesive surface property for retention, and intrinsic antibacterial defense. These principles were mechanistically translated into the design of a multifunctional wound-healing MN system as illustrated in Figure 1. To recapitulate motion mimicry, we employed SMPs combined with ML-assisted 4D printing to fabricate MNs capable of temperature-triggered deformation, enabling conformal wound closure under physiological conditions. Surface property mimicry was achieved through incorporating adhesive DNA (aDNA) resulting from complexation between polydopamine (PDA) and DNA to enhance tissue adhesion while providing sustained regenerative and angiogenic support. Functional mimicry was introduced through Zn S-PIII surface modification, imparting antibacterial protection during the early phase of wound healing. Through this integrative biomimetic strategy, our study seeks to overcome the limits of existing wound healing treatments using a novel bioinspired strategy that provides a promising versatile platform for clinical translation in skin wound repair.

2 | Results and Discussion

2.1 | Characterization of SMPs

For the fabrication of SMPs, suitable monomers and crosslinking agents are essential. In this study, tBA was employed as the monomer, and HDDA was used as the crosslinker. Photopolymerization was initiated using Omnirad 819 as the photoinitiator (Figure 2a). Upon exposure to UV light at a wavelength of 385 nm, the photoinitiator Omnirad 819 generates free radicals within the homogeneous solution containing the two acrylate components. These radicals initiate the copolymerization between the monomer and the crosslinker. The resulting SMP can be deformed into a temporary shape at temperatures above its glass transition temperature (T_g) due to the mobility of the monomer segments, while the presence of the crosslinker ensures thermal stability of the network. In this study, digital light processing (DLP), a photopolymerization-based 4D printing technique, was employed to fabricate the SMP structures. DLP employs a digital micromirror device to project light of a specific wavelength onto the resin, enabling photopolymerization over an entire area simultaneously [55, 56]. This area-based exposure approach distinguishes DLP from traditional 3D printing methods such as material extrusion (ME) and fused filament fabrication (FFF), which rely on point-by-point material deposition [12, 57–61]. In particular, DLP offers significantly higher resolution compared

to the aforementioned 3D printing techniques, making it highly suitable for applications requiring precise and detailed fabrication [62, 63]. Critical parameters in DLP-based 3D printing include light intensity, layer thickness, and exposure time, which collectively govern printing accuracy and resolution. To evaluate the performance of the fabricated SMP, the light intensity and layer thickness were fixed at 18 mW/cm² and 100 μ m, respectively. The concentration of the crosslinker HDDA was adjusted to 10, 30, and 50 wt.%, and printability was systematically investigated with respect to varying exposure times. Post-printing analysis revealed that the deviation in thickness from the original design remained within approximately 10% under all tested conditions, indicating high vertical fidelity. In contrast, the printed width remarkably increased by more than 20%, which suggests over-curing effects or lateral light scattering during polymerization (Figure S1) [64]. In this study, printing conditions that led to dimensional deviations exceeding 20% in either thickness or width relative to the designed geometry were classified as indicative of over-curing (Figure 2b).

Thermal properties of the SMPs within the printable window were evaluated using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). TGA results showed that curing time had negligible effects within the same formulation. However, the initial decomposition temperature increased with higher HDDA content, indicating enhanced thermal stability due to increased crosslink density (Figure 2c). In contrast, DSC analysis revealed that both formulation composition and curing time influenced the thermal behavior of the SMPs (Figure 2d). Specifically, the transition temperature increased with higher HDDA content, and also showed a slight increase with longer curing times, even within the same formulation. Shape recovery behavior of the produced SMPs at room temperature (RT) and 37°C was evaluated using ring-shaped specimens with a diameter of 10 mm, a thickness of 1 mm, and a height of 5 mm. Each specimen was cut at the center and subsequently placed in an oven maintained at 70°C. After keeping the samples in the oven for 2 min, a weight was put on top of the SMPs to fix a temporary flat shape at RT. Using a custom-designed jig capable of securing one end of the specimen was fabricated, as illustrated in Figure S2, for quantitative evaluation of the thermally induced shape recovering behavior of the specimen from the flat state. The specimen was fixed in the jig and subsequently immersed in water maintained at either RT or 37°C. The shape transformation behavior was then monitored under each condition to assess the temperature-responsive shape recovery characteristics. The extent of angular change was quantitatively measured using the setup described in Figure S2. As presented in Figure 2e, except for the condition with 10 wt.% HDDA cured for 2 s, the specimens exhibited a gradual change in shape over time under the test conditions. As shown in the experimental results, under the same curing time conditions, an increase in HDDA content led to a reduced degree of shape change. Conversely, under constant HDDA content, specimens cured for longer durations exhibited smaller shape changes. It was also observed that the maximum extent of shape change was dependent on the HDDA content, suggesting that the shape transformation limit can be tuned by adjusting the concentration of HDDA. This trend is attributed to the role of HDDA as a crosslinker, which increases the crosslinking density of the polymer network, thereby restricting molecular mobility and limiting macroscopic shape deformation

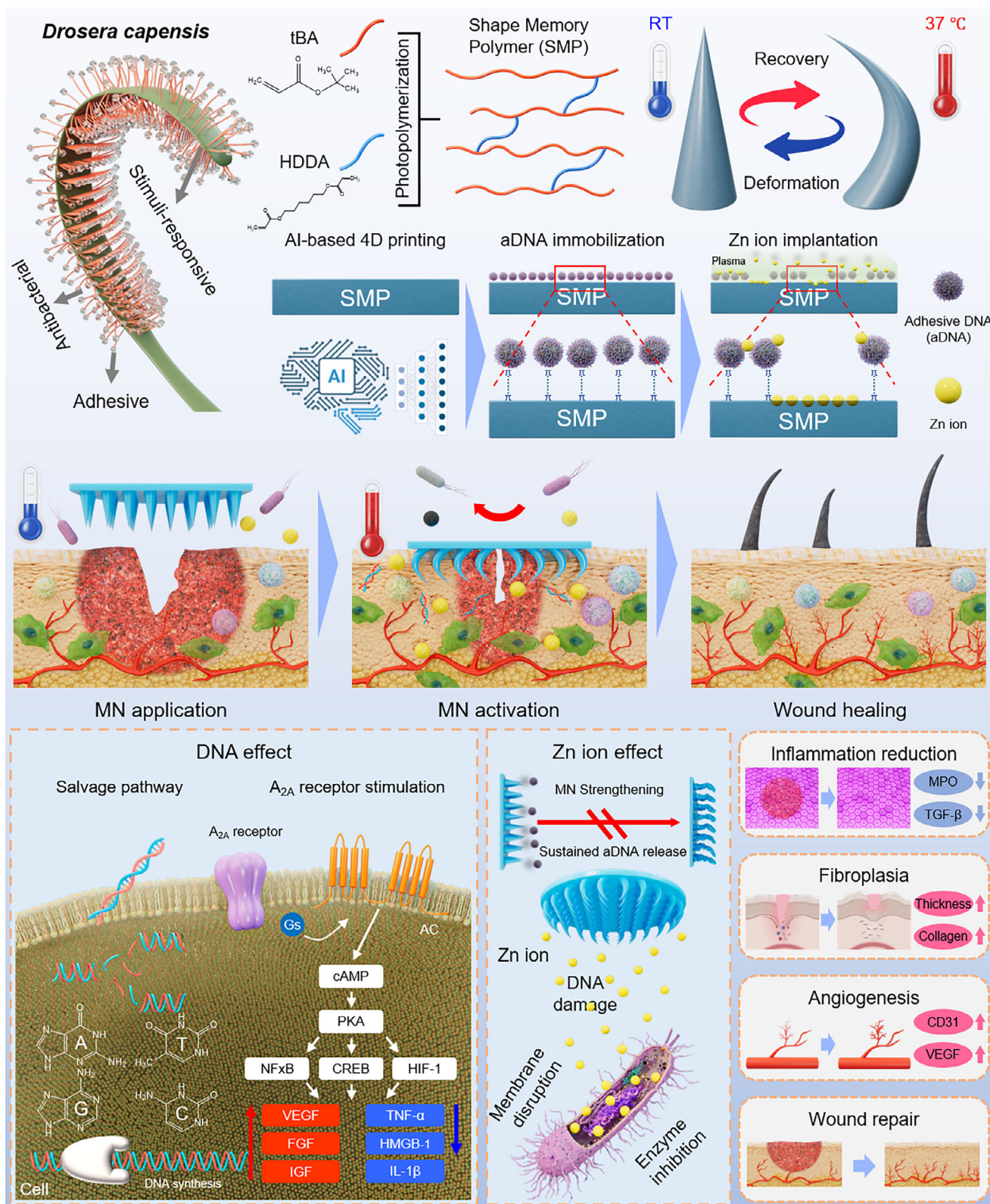


FIGURE 1 | Biomimetic shape memory MNs inspired by *Drosera capensis*. SMP MN fabrication using tert-butyl acrylate (tBA) and 1,6-hexanediol diacrylate (HDDA) via photopolymerization-based 4D printing. Thermally triggered shape recovery enables efficient skin penetration, while aDNA immobilization and Zn ion implantation synergistically promote angiogenesis, antibacterial activity, and accelerated wound healing.

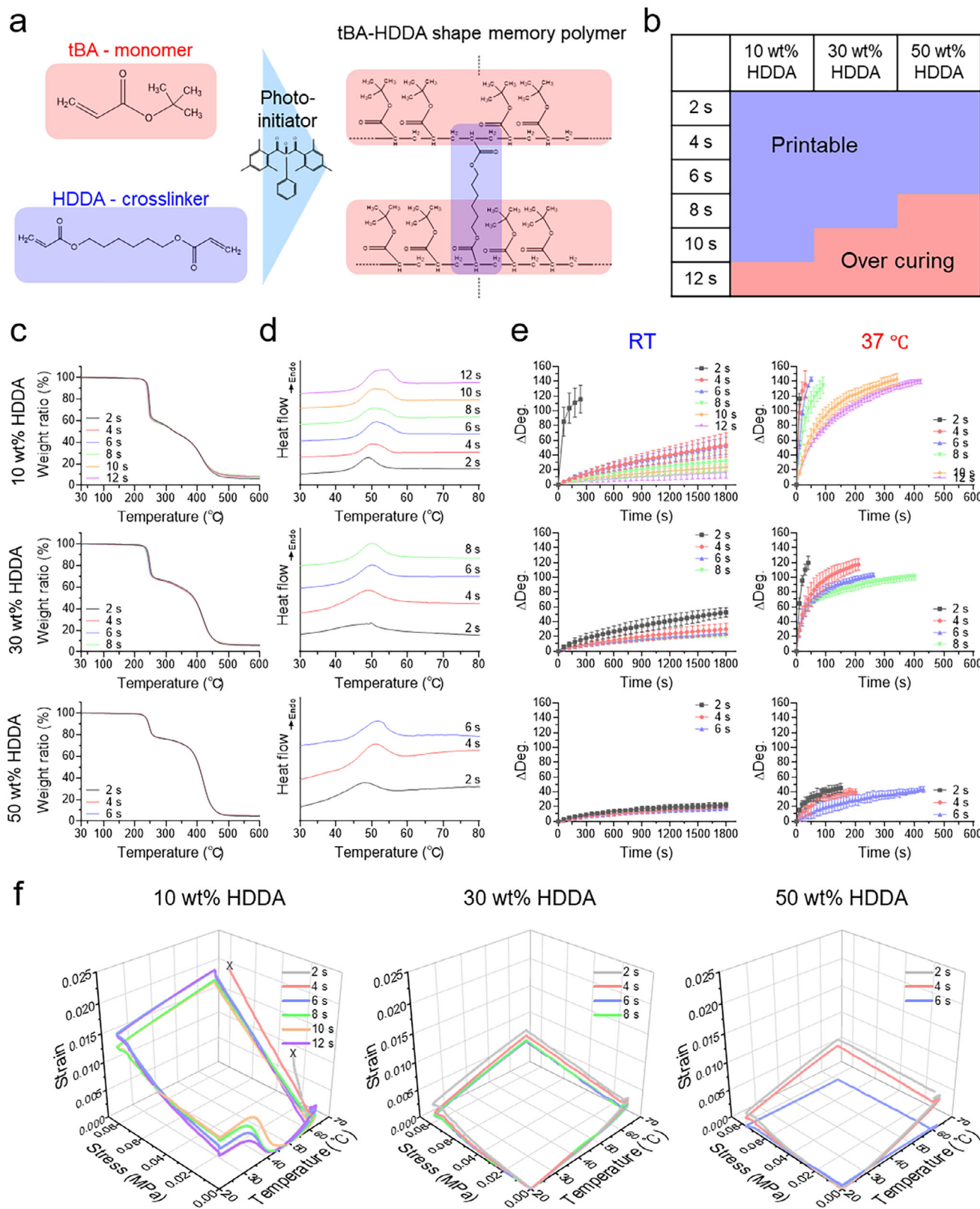


FIGURE 2 | Fabrication and characterization of SMPs. (a) Chemical structures of tBA, HDDA, photoinitiator (omnirad-819), and fabricated SMP. (b) Division of printable and over-curing conditions regarding experimental groups. (c) TGA curves and (d) DSC curves at different formulations and curing times. (e) Shape recovery behavior of the ring-shaped specimens at RT and 37°C ($N = 3$). (f) 3D thermomechanical cycle curves of fabricated SMPs.

[65]. Furthermore, environmental temperature played a significant role in shape recovery behavior. Since the fabricated SMPs undergo thermal transition upon heating, more pronounced and rapid shape changes were observed at 37°C compared to RT, indicating temperature-dependent responsiveness. In addition to the increased magnitude of angular change, the rate at which the shape transformation occurred also increased with temperature. Quantitative analysis of the average recovery rate, as presented in Figure S3, reveals that both the extent and speed of shape recovery are significantly influenced by the crosslinking density. To evaluate the shape-recovery capability of the fabricated SMPs, thermomechanical analysis (TMA) was also conducted.

Considering the three HDDA concentrations together, a coherent picture emerged of how crosslink density and curing time govern the thermomechanical and shape memory behavior of these acrylate-based SMPs (Figure 2f). At the lowest crosslink density (10 wt.% HDDA), the network behaved as a soft, highly deformable SMP with programmable large strains. Low mechanical properties of SMPs with 2 and 4 s of curing time resulted in incomplete cyclic behavior during the test (Figure S4). However, hysteresis and the breadth of the recovery transition were relatively high, especially when curing is incomplete. Progressive curing led to more homogeneous networks and sharper recovery, but even at full cure, the shape recovery remained relatively smooth and gradual. For 10 cyclic repetitions, almost identical curves were obtained which revealed structural integrity responding to temperature change. This regime is representative of lightly crosslinked SMPs in which soft-segment transitions dominate, as highlighted in recent reviews of multifunctional SMPs and 4D-printed SMP structures [66]. Increasing the HDDA content to 30 wt.% shifted the behavior toward a balanced regime where deformation capacity was reduced, but structural stability and recovery precision were enhanced (Figure 2f; Figure S5). The intermediate crosslink density allowed the material to store elastic energy efficiently while still accommodating meaningful shape changes. With longer curing times, the 30 wt.% HDDA network rapidly converged to highly repetitive thermomechanical cycles and sharp recovery profiles. This behavior aligns with experimental results showing that modest increases in crosslink density and careful control of network morphology can significantly improve recovery rate and shape fidelity without eliminating large-strain capability [67]. At the highest concentration, 50 wt.% HDDA, the network became highly constrained including limited deformation, rapid recovery, and nearly perfectly reproducible (Figure 2f; Figure S6). The sensitivity of this composition to curing time was most apparent in the transition from partially cured states, where small heterogeneities still generate detectable hysteresis, to fully cured states, where hysteresis almost vanishes, and cycle-to-cycle variation becomes negligible (Figure S6). This trend is consistent with broader evidence from photocured and 4D-printed SMP systems, where higher conversion and more uniform crosslinking directly translate into better dimensional stability and long-term durability [68]. Curing time acted as a unifying secondary parameter across all three compositions. At any given HDDA content, short curing times left a fraction of the network under-converted, resulting in higher hysteresis, broader recovery transitions, and greater cycle-to-cycle variability. Prolonged curing drove the system toward more complete conversion and a more homogeneous network, reducing energy dissipation and sharpening recovery.

Recent work on both conventional and luminescent photocured SMP systems has directly visualized this relationship, showing that curing time and conversion level strongly correlate with mechanical rigidity, shape recovery speed, and shape-memory reproducibility [68]. These findings highlight the critical role of crosslinking density in governing the dynamic shape recovery behavior of the SMP.

2.2 | ML Approach

2.2.1 | Temperature-Dependent Correlation Analysis of Shape Recovery

In this part, all analyses were performed separately for each temperature condition, since the datasets acquired at RT and 37°C differed substantially in both temporal scale and resolution. This separation allowed for the evaluation of temperature-specific correlations and model robustness without confounding effects arising from differing data distributions. To understand how each process variable influences shape recovery, pairwise Pearson correlations were first computed to establish baseline linear relationships among HDDA concentration, curing time for specimen fabrication, recovery time during shape recovering behavior, and the shape recovery ($\Delta Deg.$) at each temperature. At RT, $\Delta Deg.$ showed a moderate positive correlation with recovery time ($r = 0.650$), while both HDDA and curing time were negatively correlated ($r = -0.273$ and $r = -0.326$, respectively) as shown in Figure 3a. These relationships indicate that, under ambient conditions, shape recovery gradually occurs over recovery time but is suppressed by higher HDDA content and longer curing time, consistent with reduced polymer mobility and higher network density. At 37°C, the correlation structure changed substantially (Figure 3b). HDDA remained negatively correlated with deformation ($r = -0.649$), confirming its inhibitory role at both temperatures, whereas recovery time exhibited only a weak positive correlation ($r = 0.245$) and curing time showed a near-negligible effect on recovery behavior ($r = 0.083$). The weaker time dependence and loss of curing-time correlation at 37°C suggest that the recovery process becomes dominated by rapid thermally driven relaxation rather than gradual structural evolution, effectively decoupling recovery kinetics from curing history. Collectively, these Pearson correlation maps indicate that temperature modifies not only the magnitude but also the interdependence among variables: HDDA consistently acts as a negative regulator of shape recovery, while the contributions of recovery time and curing time diminish as the temperature approaches physiological conditions. The observed multicollinearity among HDDA, curing time, and time further underscores the need for partial correlation analysis to isolate the independent effects of each parameter.

To disentangle these coupled effects, we performed partial correlation analyses while controlling for confounding variables (HDDA, curing time, and recovery time, respectively), and then assessed statistical differences between temperature groups using Fisher's Z transformation and bootstrap resampling. Partial correlation analysis showed clear temperature-dependent trends (Figure 3c,d). When controlling for HDDA and curing time, the relationship between recovery time and $\Delta Deg.$ was markedly stronger at 37°C ($r = 0.799$) than at RT ($r = 0.587$), yielding a

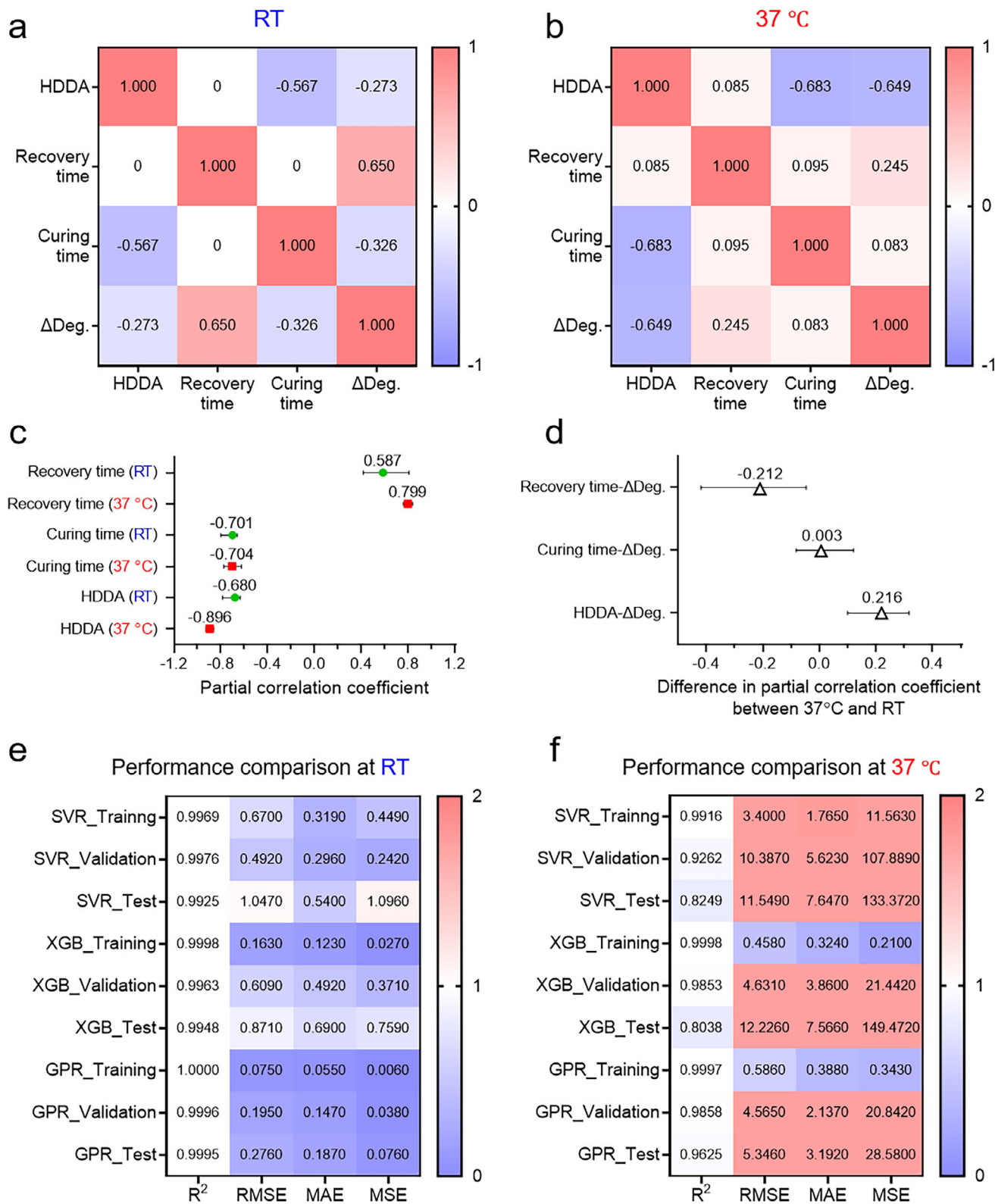


FIGURE 3 | Pearson correlation matrix at each temperature. Heatmap of correlation at (a) RT and (b) 37 °C. (c) Partial correlation coefficients between $\Delta\text{Deg.}$ and each predictor variable at two temperature conditions (RT and 37 °C). Each correlation was calculated while controlling for the other two variables. Error bars represent bootstrap 95% confidence intervals ($n = 1000$ iterations). (d) Differences in partial correlation coefficients between two temperature conditions (RT and 37 °C). Error bars represent 95% confidence intervals obtained by bootstrap resampling ($n = 1000$ iterations). Negative values indicate stronger correlations at 37 °C compared to RT. Performance comparison of each dataset (training, validation, test) of SVR, XGB, and GPR models at (e) RT and (f) 37 °C.

highly significant Fisher's Z statistic ($Z = -5.18$, $p = 2.23 \times 10^{-7}$) and a back-transformed 95% confidence interval that excluded zero (-0.53 to -0.26). Bootstrap confidence intervals confirmed the robustness of this difference (-0.38 to -0.01). This stronger temporal sensitivity implies that shape memory dynamics are more sensitive to recovery at 37°C , highlighting the need for precise control of exposure time in device applications. A similar temperature amplification was observed for the negative relationship between HDDA concentration and recovery behavior when recovery time and curing time were controlled. The partial correlation strengthened from -0.680 at RT to -0.896 at 37°C , with a significant Fisher's Z difference ($Z = 7.60$, $p = 2.86 \times 10^{-14}$) and a back-transformed CI of 0.43 to 0.65 . Bootstrap confidence intervals (0.11 to 0.27) further supported this result. This pronounced negative dependence reflects the role of HDDA as a crosslinker: higher HDDA content increases network density, limiting thermo-responsive deformation. The stronger effect at 37°C suggests that denser networks more effectively suppress thermally driven swelling at elevated temperature, likely due to restricted chain mobility. These findings emphasize that fine-tuning HDDA content is critical to control the shape memory effect. In contrast, curing time exhibited a comparable negative relationship with deformation across both temperature conditions, even after controlling for HDDA and recovery time ($r = -0.701$ at RT and $r = -0.704$ at 37°C ; $p = 0.93$). Both Fisher's Z and bootstrap confidence intervals included zero, confirming the absence of a statistically significant difference. Therefore, within the selective range, curing parameters can be adjusted for structural integrity without introducing temperature-dependent changes in the shape recovery profile. The convergence between Fisher's Z-based inference and bootstrap confidence intervals reinforces the robustness of the observed relationships and reduces concerns about non-normal residual distributions. However, caution is required because the datasets have different temporal resolution (60-second intervals up to 1800 s at RT versus 10-second intervals up to 90 s at 37°C), which may affect the magnitude of time–recovery associations. Moreover, partial correlations capture only linear effects, whereas the underlying deformation behavior is inherently nonlinear. This limitation prompted the development of nonlinear ML models to capture higher-order dependencies and cross-term effects among HDDA, curing time, and recovery time under each thermal condition.

2.2.2 | ML Model Development and Performance Evaluation

ML models were trained to predict the degree of shape recovery ($\Delta\text{Deg.}$) from HDDA concentration, curing time, and recovery time under two temperature conditions (RT and 37°C). Three regression algorithms, including Support Vector Regression (SVR), eXtreme Gradient Boosting (XGB), and Gaussian Process Regression (GPR), were developed separately for each temperature to capture the nonlinearity and temperature dependence of the recovery process. Model accuracy was evaluated using the coefficient of determination (R^2), root-mean-square error (RMSE), mean-absolute error (MAE), and mean-square error (MSE). The results are summarized in Figure 3e,f and visualized in Figure S7, which show predicted versus actual values for the training, validation, and test sets.

At RT, all three models demonstrated excellent predictive performance. The SVR model achieved $R^2 = 0.9969$, 0.9976 , and 0.9925 for the training, validation, and test sets, respectively, with RMSE values of 0.6700 , 0.4920 , and 1.0470 (Figure 3e). The XGB model yielded comparable accuracy across the three datasets, indicating a strong ability to model nonlinear parameter interactions (Figure 3e). The GPR model provided the highest accuracy overall (Figure 3e). In addition, GPR supplied predictive uncertainty estimates, with mean $\sigma \approx 0.13$, 0.16 , and 0.18 for the respective datasets, demonstrating both exceptional precision and high confidence in its predictions. At 37°C , prediction accuracy decreased slightly due to the narrower temporal range (0 – 90 s) and fewer data points but remained strong. The SVR model achieved $R^2 = 0.9916$, 0.9262 , and 0.8249 , with RMSE = 3.4 , 10.3870 , and 11.5490 for training, validation, and test sets, respectively (Figure 3f). The XGB model showed improved consistency, and the GPR model again produced the most reliable performance among all models (Figure 3f). Importantly, its mean predictive uncertainty (σ) increased from ~ 1.41 to ~ 2.46 as the dataset shortened in duration, reflecting the higher intrinsic variability of rapid recovery at physiological temperature. Across both temperatures, GPR consistently outperformed SVR and XGB in terms of R^2 , RMSE, and MAE, particularly on unseen test data. Its probabilistic kernel framework efficiently interpolated sparse regions of the dataset and quantified uncertainty in the predictions, making it ideal for limited or unevenly sampled experiments. XGB offered comparable accuracy and better interpretability through feature-importance analysis, which identified recovery time as the dominant positive predictor at 37°C and HDDA concentration as the most significant negative contributor at RT. In contrast, SVR showed slightly lower generalization due to its sensitivity to parameter scaling and kernel bandwidth selection. The overall higher prediction accuracy of all models at RT compared to at 37°C arises from the longer observation window (up to 1800 s), which allowed the learning of full recovery behavior. Conversely, the shorter 37°C dataset (up to 90 s) captured only the rapid initial response, limiting temporal information and increasing residual variance. Despite these challenges, all models successfully reproduced the experimentally observed trends: recovery increased with time but decreased with HDDA content and curing time, consistent with the polymer-network dynamics inferred from the correlation analysis. These results demonstrate that nonlinear ML frameworks can accurately and reliably shape recovery in 3D-printed MNs from a limited dataset. Specifically, GPR provided the providing predictive means and confidence intervals, offering an optimal balance between accuracy and interpretability. These models establish a quantitative basis for parameter-controlled optimization of SMP formulations, enabling reliable extrapolation to new compositions (e.g., HDDA 5 and 20 wt.%) with uncertainty quantification in section 2.2.4.

2.2.3 | Feature Importance

To further interpret the trained models, permutation-based feature importance analyses were performed for SVR, XGB, and GPR under both temperature conditions (RT and 37°C) as shown in Figure S8. Across all models, HDDA concentration, curing time, and recovery time contributed distinctively to the prediction of $\Delta\text{Deg.}$ with notable temperature-dependent variations in their relative impact. At RT, all three models showed comparable

feature hierarchies: recovery time exhibited the highest relative importance ($SVR = 1.17 \pm 0.11$, $XGB = 1.21 \pm 0.11$, $GPR = 1.22 \pm 0.11$), followed by HDDA (1.02–1.10 range) and curing time (0.84–0.93). This indicates that, under ambient conditions, shape memory behavior is primarily governed by the time-dependent viscoelastic relaxation behavior, while crosslink density (controlled by HDDA) acts as a secondary inhibitor. The moderate contribution of curing time suggests that the network formation process influences shape memory effect indirectly through its effect on polymer stiffness rather than kinetic recovery behavior. At 37°C, the trend of permutation importance changed markedly, reflecting thermally accelerated recovery behavior. HDDA exhibited a dramatic increase in importance across all models ($SVR = 5.52 \pm 1.09$, $XGB = 4.08 \pm 0.78$, $GPR = 5.52 \pm 1.09$), surpassing both recovery time and curing time. This shift implies that at physiological temperature, network crosslink density becomes the dominant limiting factor for recovery, as thermal activation amplifies swelling and segmental motion but denser HDDA-rich networks resist such expansion. Curing time also gained moderate importance ($SVR = 2.42 \pm 0.76$, $XGB = 1.39 \pm 0.28$, $GPR = 2.42 \pm 0.76$), likely due to enhanced structural relaxation in partially cured networks, while the relative contribution of recovery time decreased ($SVR = 1.28 \pm 0.44$, $XGB = 1.19 \pm 0.38$, $GPR = 1.28 \pm 0.44$). These trends align with Fisher's Z-based partial correlation analysis, which showed a pronounced increase in HDDA- ΔDeg dependence at 37°C, indicating stronger thermomechanical coupling under elevated temperature.

The feature-importance analysis establishes a coherent physical interpretation consistent with polymer network mechanics. At RT, the shape recovery is time-governed, dominated by gradual viscoelastic relaxation, whereas at 37°C, it becomes structure-governed, constrained by crosslink density and chain mobility. The convergence of results across all three algorithms (SVR, XGB, GPR) underscores the robustness of these findings and confirms that each model captures complementary aspects of the same physical process—temporal evolution versus network constraint. Moreover, the GPR model, by integrating predictive uncertainty with feature relevance, provides additional insight into how temperature modulates parameter sensitivity, suggesting that future models can benefit from physics-informed kernel structures incorporating temperature-dependent relaxation functions or Arrhenius-type scaling.

2.2.4 | Model Generalization and Prediction of New Datasets

To evaluate the generalization capability of the trained models, independent datasets were introduced at both RT and 37°C, consisting of new combinations of HDDA concentration and curing time that were not included in the training stage. At RT, the new samples including 5 and 20 wt.% HDDA were prepared with curing times of 4, 6, 8, 10, and 12 s, whereas at 37°C, samples with 20 wt.% HDDA with curing times of 2, 4, and 6 s were tested. These datasets were used to predict the ΔDeg using the previously optimized SVR, XGB, and GPR models, and the results were compared with the experimentally measured values (Table S1 and Figure 4). Each individual time-dependent data set was converted into an indexed format (sample index) to enable simultaneous

visualization of the datasets under the 5 and 20 wt.% conditions within a single plot as demonstrated in Figure 4.

All three models successfully captured the recovery trend across the new formulations, though their predictive fidelity varied by algorithm and temperature. At RT, the SVR model maintained strong performance with $R^2 = 0.9475$, $RMSE = 2.98$, $MAE = 2.26$, and $MSE = 8.91$, accurately reproducing both the magnitude and temporal profile of recovery (Figure 4a). The XGB model achieved $R^2 = 0.8451$ and $RMSE = 5.13$, slightly underperforming SVR but still preserving the nonlinear shape of the deformation curves, suggesting that boosting ensembles retained robustness when extrapolating to unseen curing-time regimes (Figure 4c). The GPR model exhibited the best agreement with experiments ($R^2 = 0.9625$, $RMSE = 2.52$, $MAE = 1.71$, $MSE = 6.37$), and its 95% confidence intervals consistently enclosed the true experimental data, validating its uncertainty quantification capability and excellent interpolation between distinct HDDA concentrations (Figure 4e). At 37°C, predictive accuracy declined for all models owing to the highly nonlinear, rapid deformation behavior at physiological temperature. The SVR model achieved $R^2 = 0.7453$ and $RMSE = 13.38$, with a tendency to underpredict near-peak deformation values (Figure 4b). The XGB model showed limited generalization ($R^2 = 0.0689$, $RMSE = 25.57$), indicating that its tree-based partitions could not fully capture the abrupt kinetics of shape recovery behavior under accelerated relaxation conditions (Figure 4d). In contrast, the GPR model preserved moderate predictive power ($R^2 = 0.6640$, $RMSE = 15.36$, $MAE = 12.32$), while providing uncertainty bounds that expanded proportionally with increased thermal fluctuation, as reflected in a mean $\sigma \approx 2.46$ (Figure 4f). Although quantitative accuracy was reduced, the predicted mean curves and credible intervals faithfully traced the qualitative experimental trends, demonstrating the model's capability to represent high-temperature stochasticity. These results reveal that temperature strongly affects model generalization, not only by altering shape memory kinetics but also by reducing data density in the temporal domain. The GPR framework demonstrated superior resilience to such variability through probabilistic regression, providing both accurate predictions and interpretable uncertainty bands. Conversely, deterministic models such as SVR and XGB, while effective at RT, showed decreased extrapolation reliability at 37°C due to overfitting to low-temperature dynamics. These outcomes highlight the critical importance of incorporating physical priors, such as polymer relaxation times and crosslink density effects, into the ML pipeline, suggesting that physics-informed GPR or hybrid digital-twin frameworks could further enhance predictive transferability across temperature regimes.

The integration of ML in this study offers several strategic advantages over conventional AI-assisted bioprinting frameworks. While previous studies have primarily focused on enhancing static structural fidelity or process-specific printability [51–54], our work extends the application of ML to the dynamic, thermo-responsive domain of 4D constructs. By modeling the complex interplay between material composition, curing kinetics, and thermal recovery, the GPR model provided a robust predictive map that surpasses simple empirical optimization. Importantly, beyond algorithmic performance comparison, this predictive robustness establishes a quantitative basis for translating material-level recovery behavior into device-level shape

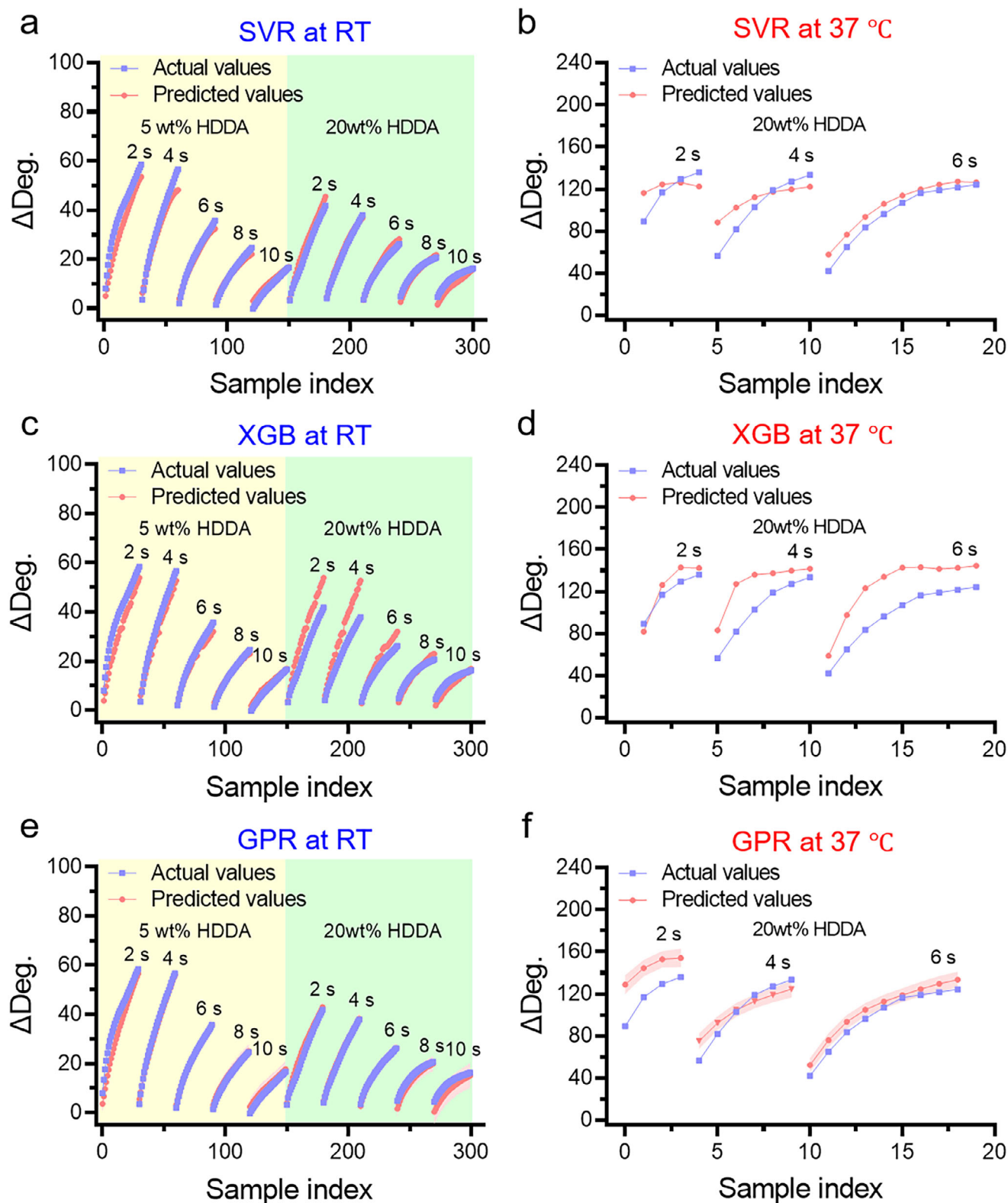


FIGURE 4 | Model generalization performance on new experimental datasets. (a) SVR at RT, (b) SVR at 37°C, (c) XGB at RT, (d) XGB at 37°C, (e) GPR at RT, and (f) GPR at 37°C. The blue lines denote experimental values and the red lines represent predicted values; shaded regions (for GPR) indicate 95% confidence intervals. All models reproduced the deformation trajectory across new curing-time and HDDA conditions, with GPR showing the highest fidelity and uncertainty awareness.

recovery design. Because angular recovery ($\Delta Deg.$) directly governs the bending amplitude and shape recovery strength in the MN architecture, it was adopted as a device-relevant performance metric linking material behavior to device function. The ML model incorporated HDDA concentration (material), curing time (process), and recovery time (shape recovery) as input variables, thereby establishing a comprehensive material–process–shape recovery response landscape. Within this landscape, the 10 wt.% HDDA with 6 s of curing time was strategically selected as the optimal fabrication window for MN, exhibiting the most favorable balance between thermo-responsive recovery and the mechanical stability required for MN recovery. This data-driven approach allowed the MN to transition from a passive scaffold to an active mechanical actuator for wound closure, representing a more intelligent approach to wound management compared to single-modality platforms.

2.3 | Mechanical and Cellular Responses of SMPs

Tensile and compressive properties were evaluated using SMPs fabricated within the processable range. As shown in Figure S9, the 10 and 30 wt.% HDDA specimens exhibited a non-typical tensile behavior compared to conventional polymer samples. Specifically, the stress increased linearly with strain, followed by a sharp drop after the peak stress, and then a secondary increase before final fracture. Although the 50 wt.% HDDA specimens displayed some similar features, its overall tensile behavior more closely resembled that of general polymeric materials. Quantitative analysis revealed that for the 10 wt.% HDDA condition, the ultimate tensile strength (UTS) increased sharply from 2.0 to 17.9 MPa as the curing time increased from 2 to 8 s, after which the UTS plateaued with no statistically significant differences (Figure S10). A similar trend was observed in the modulus values, which showed a sharp increase from 1.6 to 481.8 MPa with increasing curing time, followed by a saturation. In contrast, the elongation at break exhibited a different pattern. Relatively high elongation values were observed at 2 and 4 s curing conditions, but after 6 s of curing, the values remained relatively constant until a noticeable decrease was observed at the 12 s curing condition. For the 30 wt.% HDDA condition, the UTS increased from 7.8 MPa at 2 s of curing to 20 MPa at 6 s, while the tensile modulus also rose substantially from 23.7 to 530.7 MPa. In this condition, elongation at break showed an increasing trend with curing time, rising from 29.4% to 39.1% up to 6 s. In contrast, for the 50 wt.% HDDA condition, both UTS and tensile modulus increased with curing time (2 to 6 s) from 13.8 to 21.9 MPa and from 264.6 to 522.3 MPa, respectively. On the other hand, elongation at break exhibited a decreasing trend, dropping from 16.7% to 13.3% as curing time increased from 2 to 6 s. Compressive properties were also assessed following different printing conditions. Figure S11 demonstrates representative compressive stress–strain curves of three different solution formulations. Except for 2 s of curing time, compressive stress–strain curves exhibited a similar trend regardless of compositional change. However, increasing HDDA contents in photopolymerizable solution, compressive properties including compressive yield strength and compressive modulus, tended to increase at identical composition. Considering the enhanced compressive properties following compositional change at the same curing time, crosslinking density between tBA and HDDA is

a crucial factor for determining mechanical properties. Figure S11 shows the compressive stress–strain behavior of samples cured at various conditions for different curing times. As the curing time increased, the initial slope of the stress–strain curve, representing the compressive modulus, increased significantly up to a certain point, and the change became negligible. This indicates that the degree of crosslinking within the polymer network increases with curing time. In the early stages of curing, all three formulations (10, 30, and 50 wt.% HDDA) showed a pronounced increase in yield compressive strength and modulus, suggesting effective crosslink formation. As demonstrated in Figure S12, compressive yield strength and compressive modulus were quantitatively compared among the experimental conditions. In 10 wt.% HDDA condition, compressive yield strength, and compressive modulus increased from 12.9 and 145.0 MPa for 2 s of curing to 29.2 and 287.8 MPa for 6 s of curing, respectively. After 6 s, compressive properties became plateaued at similar values. On the other hand, preserved compressive properties were monitored in 30 wt.% HDDA condition from 4 s of curing with 31.7 MPa of compressive yield strength and 328.8 MPa of compressive modulus, whereas 28.2 MPa of compressive yield strength and 284.5 MPa of compressive modulus were recorded in the 2 s curing group. Compared to other formulations, 50 wt.% HDDA showed similar compressive properties until an increasing trend was observed for 6 s curing. These increases in tensile and compressive properties are mainly attributed to the enhanced degree of crosslinking between tBA and HDDA [69].

Considering the printability and processability, 10 wt.% HDDA condition was focused on for further experiments. Within the printable region, as demonstrated in Figure 2b, biological properties were assessed in terms of in vitro cell attachment and proliferation. Since diabetic wound healing is mainly dominated by vascular endothelial cells and fibroblasts, responses of both cells were compared following different curing times [70, 71]. The in vitro evaluation of human umbilical vein endothelial cells (HUVECs) and NIH3T3 fibroblasts revealed that cells cultured on the specimens with 4 to 10 s of curing time exhibited similar morphology, whereas distinct differences were observed at the specimens cured for 2 and 12 s. Proliferation of HUVECs on the prepared specimens was compared by CCK-8 assay. As illustrated in Figure S13, endothelial cells displayed round morphologies with restricted spreading and minimal protrusions in the specimen with a curing time of 2 s. In the intermediate range (curing time between 4 and 10 s), cells showed broader spreading and more developed filopodia, which are important for establishing vascular structures. Nevertheless, at 12 s, cells appeared aggregated or clustered, indicating impaired adhesion and potential cellular stress. Quantitative analysis of proliferation rate further supported these findings, showing relatively stable values for adhesion- and spreading-related metrics at specimens with 4–10 s of curing time, while the degree of proliferation decreased on the 2 and 12 s curing conditions. From the perspective of wound healing, these results are particularly relevant. Early wound repair relies on coordinated endothelial sprouting to form provisional tissue and new vasculature and fibroblast migration. The impaired responses observed at 2 and 12 s in the cured specimen suggest insufficient surface characteristics to initiate such processes [12, 72, 73]. A comparable trend was observed for NIH3T3 fibroblasts (Figure S14). Field-emission scanning electron microscopy (FESEM) images demonstrated

that cells cultivated on the specimen with 2 s curing exhibited limited spreading and relatively sparse intercellular connections, indicating suboptimal adhesion. Similarly, fibroblasts remained less spread compared with intermediate conditions (4 s curing). In contrast, well-spread fibroblasts with extensive filopodia and reticular networks were observed on 6 to 10 s cured specimens, suggesting favorable conditions for fibroblast migration and interaction [74–76]. However, at 12 s curing, network density decreased, and cell morphologies became more heterogeneous. Taken together, these findings indicate that moderate curing time (6 to 10 s) provides optimal conditions for cell adhesion and network formation, while insufficient (2 to 4 s) or excessive (12 s) curing may compromise the cellular responses required for effective wound healing.

2.4 | MN Fabrication and Shape Recovery Behavior

The morphological design and mechanical performance of the shape-programmed MNs were systematically evaluated. Figure 5a shows the sequential fabrication of MNs with varying curvatures, from straight conical to highly curved geometries. The initial 3D models were faithfully replicated in the fabricated structures, demonstrating the feasibility of precisely controlling the needle curvature through the design parameters. The resulting MNs exhibited well-defined shapes and consistent reproducibility across multiple arrays, confirming the reliability of the fabrication process. However, the degree of curvature was rather decreased in printed MNs compared to the initial design because of the limitations of constructing a freeform structure [77]. The bending and shape recovery behaviors of the MNs under aqueous conditions with different temperatures were further investigated (Figure 5b and Video S1). The curved MNs displayed reversible bending motion upon thermal stimuli with the motion sequence visualized over time. Prior to placing curved MNs in the water, MNs were straightened at an increased temperature at 70°C. At RT, flattened MNs slightly recovered its shape after 240 s. However, it could not recover its original shape within the short time which is required in soft tissue fixation. On the other hand, MNs placed in the water at 37°C recovered fast within 240 s, and they reached their original shape within 120 s of immersion. The difference in shape recovery behavior under two distinct temperature conditions was clearly observed by comparing the initial state (white dashed lines) with the final state (red dashed lines) in Video S1. This highlights their potential for penetration and mechanical interlocking with soft substrates [78, 79]. Another important issue for MNs for tissue fixation is their resistance to wound opening [80]. For measuring the resisting force, a weight-lifting test was conducted as demonstrated in Figure S15.

Volumetrically 1000 times enlarged MNs were prepared under identical printing conditions, and MNs were flattened with the same procedure. Different weights were attached to the tip of the MNs, and they were heated using a heat gun. Weights from 100 mg to 50 g were utilized, and MNs could not recover their initial shape when 50 g of weight was utilized. Thus, it could be assumed that the resisting force of MNs for wound opening is 0.49 N which is identical to the gravitational force of 50 mg. Considering that the force required to stretch murine skin by

3 mm is less than 0.5 N, the force generated by the enlarged needle is within a comparable range to that required for closing an incisional wound [81]. Thus, considering the size of the MNs, it is sufficiently strong for wound closure. Such mechanical adaptability is also advantageous for other biomedical applications where stable interfacing with tissues is essential [82–85].

2.5 | Preparation of aDNA

The morphological and physicochemical characteristics of the aDNA were systematically analyzed. Cryo-transmission electron microscopy (cryo-TEM) images confirmed the formation of uniformly dispersed nanoscale particles with spherical morphology and an average diameter of approximately 5 nm (Figure 5c). The formation of aDNA is governed by a synergistic interplay of oxidative polymerization and multivalent interfacial interactions. Initially, dopamine undergoes oxidative self-polymerization in a mildly alkaline Tris–HCl buffer (pH 8.5), forming PDA nanoparticles enriched with catechol, quinone, and amine functional groups. Upon introduction of DNA into the PDA nanoparticle suspension, spontaneous hybridization occurs without the need for external crosslinkers [12, 86]. The negatively charged phosphate backbone of DNA interacts with functional groups on the PDA surface through electrostatic attraction and charge redistribution, while aromatic indole structures in PDA promote π – π stacking with nucleobases. Simultaneously, hydrogen bonding between catechol/quinone moieties and DNA further stabilizes the interface, and possible Schiff base or Michael-type reactions between oxidized quinones and nucleophilic groups on DNA may contribute to additional stabilization. These multivalent interactions anchor DNA strands onto the nanoscale PDA cores, suppressing long-range entanglement of extended DNA ribbons and inducing conformational compaction. As a result, a core–shell nanostructure is formed in which PDA constitutes the inner core, and DNA forms a negatively charged outer corona. This structural reorganization accounts for the reduced hydrodynamic size and the pronounced shift toward a more negative zeta potential. The developed aDNA system represents a stable, well-dispersed hybrid nanostructure generated through mussel-inspired adhesive chemistry and cooperative secondary interactions. The inset illustrates a schematic reconstruction of the particle surface, further supporting the high degree of structural homogeneity and controlled size distribution. These results demonstrate the successful bottom–up assembly of DNA into stable nanostructures, which is consistent with recent reports on DNA nanotechnology for biomedical applications [12]. Dynamic light scattering (DLS) measurements further validated the particle size distribution and monodispersity (Figure 5d). Distinct peaks corresponding to different molecular components including PDA, DNA, and aDNA, indicated successful encapsulation and hierarchical assembly of DNA with supporting carrier matrices. The sizes of PDA, DNA, and aDNA analyzed by DLS were noted as 25.4 ± 3.6 , 11.2 ± 2.9 , and 5.1 ± 0.7 nm, respectively. A decrease in the size of aDNA compared to PDA and DNA was because of charge screening between two molecules [12]. For confirming charge screening, the zeta potential of each molecule was measured, and -12.4 ± 0.8 mV for PDA, -32.5 ± 0.9 mV for DNA, and -0.2 ± 1.2 mV for aDNA of zeta potential was observed (Figure 5e). The narrow polydispersity index suggests high reproducibility of the synthesis process, in line with recent

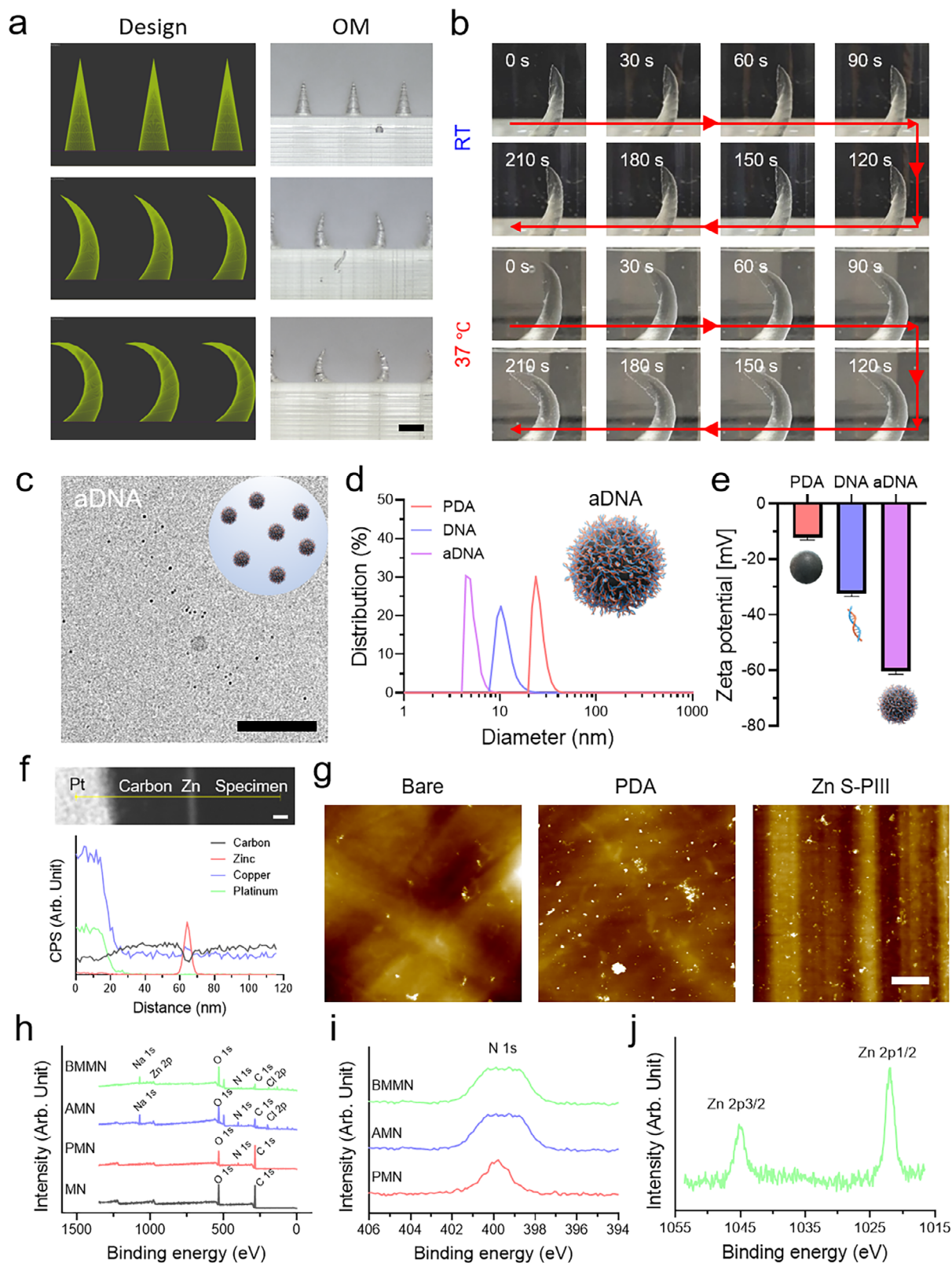


FIGURE 5 | Fabrication and characterization of surface-treated MN patches. (a) 2D designs and optical images of MNs with different curvatures (scale bar: 500 μm). (b) Time-lapse shape recovery behavior of 1000 times volumetrically enlarged MNs at RT and 37°C. (c) Cryo-TEM image of produced aDNA (scale bar: 100 nm). (d) Size distribution and (e) zeta potential of PDA, DNA, and aDNA ($N = 3$). (f) Cross-sectional STEM image and STEM-EDS elemental analyses with carbon, zinc, copper, and platinum (scale bar: 10 nm). (g) Representative AFM images of bare, PDA, and ZnS-PIII-treated specimens (scale bar: 2 μm). XPS analyses with (h) overall range and (i) N 1s focused range. (j) Zn XPS result of BMMN.

findings on optimized nucleic acid nanostructures for therapeutic delivery.

2.6 | Physiological Characterization After Zn S-PIII Treatment

Even though aDNA-immobilized MNs are beneficial to wound healing, the wound site is vulnerable to infection due to the invasion of bacteria [87–89]. As a way to suppress infection during wound healing procedure, various strategies have been invented including the incorporation of additional antibacterial molecules and coatings [83, 90, 91]. However, conventional coating methods are not suitable for prolonged attachment to tissues due to possible detachment of the coating. Thus, there has been increasing interest in the ion implantation technique to polymeric matrices. Especially for metal ion implantation, sputtering-based plasma immersion ion implantation (S-PIII) technique showed superior stability compared to metal coating methods [73, 92–94]. In this study, we utilized the Zn S-PIII technique to assign antibacterial properties and enhanced surface hardness. The structural and compositional characterization of specimens after Zn S-PIII treatment were first investigated. As shown in Figure 5f, a clear Zn layer within 10 nm was shown in the STEM image. Energy-dispersive X-ray spectroscopy (EDS) confirmed the distribution of Zn, C, Cu, and Pt along the cross-section. Excluding Cu and Pt resulting from the preparation process including the TEM grid and Pt coating, carbon was homogeneously distributed in the analyzed region. However, a notable peak of Zn was observed corresponding to a bright line in the STEM image. Surface morphology was further examined by atomic force microscopy (AFM), revealing nanoscale roughness and well-aligned topographic features across different scanning regions (Figure 5g).

Overall, X-ray photoelectron spectroscopy (XPS) analysis was further conducted for MN, PDA coated MN (abbreviated as PMN), aDNA-immobilized MN (abbreviated as AMN), and biomimetic MN (abbreviated as BMMN; ZnS-PIII-treated aMN) samples (Figure 5h). The peaks corresponding to polymeric backbones and Zn-related moieties were clearly observed in experimental groups. N 1s, Na 1s, and Cl 2p peaks were additionally observed in the AMN group which was derived from a combination of PDA and DNA salt. In concentrated XPS analyses for N and Zn elements, distinctive N 1s and Zn 2p peaks were observed in the binding energy range near 400 eV, and 1015–1045 eV, respectively. Since PDA is composed of C, N, and O elements, the N 1s peak is conventionally utilized for confirmation of PDA coating as illustrated in Figure 5i [95–97]. After Zn S-PIII treatment, the Zn 2p peak appeared, and the intensity of O 1s increased, whereas the intensity of C 1s decreased (Figure 5h,j). Along with Zn ion implantation, the intensity of O 1s increased due to the formation of ZnO on top of the surface [94]. The surface wettability analysis demonstrated a considerable difference in hydrophilicity between the two groups (Figure S16). The aDNA and Zn S-PIII-treated sample exhibited a reduced water contact angle compared to the bare sample, indicating enhanced surface hydrophilicity. Improved wettability has been closely associated with better protein adsorption and subsequent cell adhesion, thereby playing a pivotal role in biomaterial–tissue interactions [7, 98].

Nanoindentation mapping revealed distinct hardness distribution profiles across the investigated surfaces (Figure S17a). The 3D contour and corresponding FESEM images indicated that the Zn S-PIII-treated surface possessed a more uniform hardness profile, whereas the bare specimen exhibited localized heterogeneity with sharp gradients. This improvement in homogeneity can be attributed to refined microstructural features and the elimination of surface irregularities. Detailed FESEM observations of indentation imprints (Figure S17a) further confirmed differences in deformation mechanisms. The bare surface showed irregular pile-up and crack propagation around the indentation site, whereas the treated surface maintained well-defined indent edges with minimal crack formation. These results suggest that the treatment improved resistance to plastic deformation and reduced defect-induced stress localization [99]. Quantitative analysis of indentation lengths and calculated hardness values revealed that the treated samples exhibited significantly higher hardness compared to the bare specimen, as shown in Figure S17b,c. Due to the presence of Zn ion nanolayer on top of the surface, resistance against compression load of the Zn S-PIII treated surface was increased as shown in Figure 6a. After the same load was applied, the monitored depth was smaller in the Zn S-PIII-treated specimen. Mechanical properties of MNs with and without Zn S-PIII treatment were systematically evaluated through compression testing (Figure 6b). The compression load-displacement curves demonstrated that the MNs maintained structural stability under increasing loads, with curved geometries showing enhanced mechanical resilience compared to straight ones. Even though a slight increase in load/needle was monitored in Zn S-PIII-treated MNs, it is notable that no obvious detrimental effect of the ion implantation process was observed as demonstrated in Figure 6b.

2.7 | Antibacterial of Zn S-PIII Treated MNs

The antibacterial activity of the Zn ion-implanted MN patches was systematically evaluated against both *Escherichia coli* (*E. coli*, Gram-negative) and *Staphylococcus aureus* (*S. aureus*, Gram-positive), as shown in Figures S21 and S22. In the case of *E. coli*, a dense distribution of bacterial colonies was observed in the flat, MN, and AMN groups, while a remarkable reduction in colony number was evident in the BMMN group (Figure S21). Quantitative analysis confirmed that BMMN reduced colony formation by more than 80% compared to the flat surface (Figure S21), highlighting its potent antibacterial efficacy [100–102]. A similar trend was observed for *S. aureus*, where flat and MN groups exhibited negligible antibacterial effects, and AMN showed only moderate inhibition as demonstrated in Figure S22. In contrast, BMMN demonstrated significant antibacterial activity, reducing bacterial colonies to a minimal level. These antibacterial properties indicate that the incorporation of Zn ions played a crucial role in broad-spectrum antibacterial efficacy [103, 104]. Zn ions are known to disrupt bacterial cell membranes, interfere with metabolic enzymes, and induce reactive oxygen species (ROS) generation, leading to bacterial death [105, 106]. Unlike conventional Zn coating methods, the Zn S-PIII technique forms a stable Zn-based nanolayer on the surface while introducing a relatively lower total amount of Zn. This controlled surface modification enables sustained and regulated Zn ion release rather than excessive burst release. A study on a biliary stent fabricated using the same Zn S-PIII technology also reported that

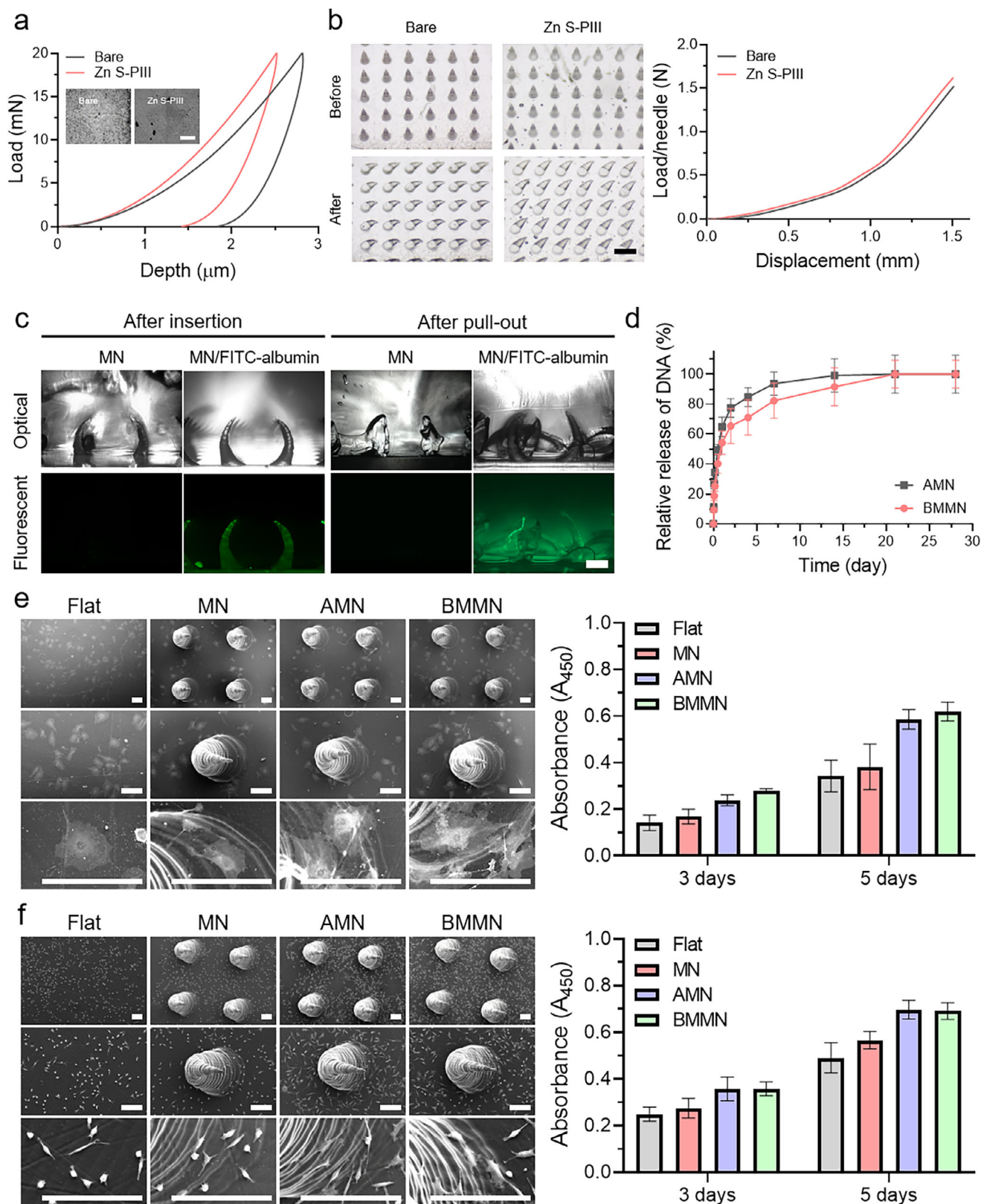


FIGURE 6 | Mechanical properties and cellular responses of biomimetic MNs. (a) Obtained load-depth curve during indentation procedure and traces after indentation (scale bar: $5\ \mu\text{m}$). (b) Optical images of MNs before and after compression (scale bar: $1\ \text{mm}$) and measured load/needle following increasing displacement. (c) Optical and fluorescent images of MN and MN/FITC-albumin after insertion and pull-out (scale bar: $500\ \mu\text{m}$). (d) Relative release profile of DNA from AMN and BMMN ($N = 3$). (e) Representative images of attached HUVECs at 1 day and the degree of HUVEC proliferation at 3 and 5 days of culturing ($N = 3$, scale bar: $200\ \mu\text{m}$). (f) Representative images of attached fibroblasts at 1 day and the degree of fibroblast proliferation at 3 and 5 days of culturing ($N = 3$, scale bar: $200\ \mu\text{m}$).

Zn ion release was sufficiently controlled to achieve antibacterial efficacy while maintaining favorable tissue regeneration outcomes [94]. Considering the enhanced cellular responses against MN patches, BMMN provides a dual benefit of effective bacterial inhibition and potential wound healing acceleration.

2.8 | DNA Delivering Capability and In Vitro Biocompatibility of MNs

The delivering capability of biomolecules was assessed using fluorescein isothiocyanate–conjugated albumin (FITC-albumin) and UV–Vis spectroscopy. In Figure 6c, MNs maintained their curved geometry upon insertion into agarose hydrogel, while fluorescence images confirmed localized distribution of the loaded biomolecules along the curved tips. After elimination of MNs, green fluorescence was monitored in the hydrogel which reveals biomolecule delivery. DNA delivery from MNs was also compared between the AMN and BMMN groups. As illustrated in Figure 6d, DNA was released for 2 weeks in AMN which is comparable to the results of a previous study [12]. On the other hand, prolonged release of DNA was monitored in ZnS-PIII-treated specimens. This phenomenon was attributed to the altered release path by the metal nanolayer [73, 94]. This prolonged release behavior was primarily governed by the Zn ion–implanted nanolayer deposited on the AMN [94]. Implantation of heavy ions into polymeric matrix generates compressive stress within the polymer matrix, decreasing interchain distance and promoting structural densification [92]. The resulting compact and metal-embedded nanosurface serves as a physical and energetic barrier to DNA diffusion. In addition, the ROS scavenging ability of aDNA incorporated MNs was evaluated by H₂O₂ and ABTS assay (Figures S18 and S19). Both AMN and BMMN groups exhibited substantial H₂O₂ scavenging activity. In agreement with these findings, ABTS radical inhibition was significantly enhanced in the aDNA incorporated groups relative to the flat, with BMMN achieving the highest antioxidant capacity. This ROS scavenging ability of AMN and BMMN is highly efficient to tissue regeneration since the generation of ROS in the wound results in delaying re-epithelialization, elongating the inflammatory phase, and restraining angiogenesis [100, 107].

Surface interactions with cells were assessed by FESEM observation after seeding HUVECs and fibroblasts on the MN substrates (Figure 6e,f). As shown in Figure 6e, HUVECs on the flat surface exhibited relatively limited attachment, with rounded morphologies and few filopodial extensions. In contrast, cells grown on the MN surface displayed noticeably greater spreading with elongated cytoskeletal protrusions along the curved needle architecture. These topographical cues provided by the three-dimensional MN geometry appear to facilitate focal adhesion formation and cytoskeletal organization, consistent with the notion that nanoscale curvature and microscale roughness enhance cell–substrate interactions [108, 109]. The highest proliferation rate in the BMMN group reflects the synergistic contribution of physical topography, DNA-mediated adhesion, and Zn-induced pro-angiogenic signaling. These combined effects created a favorable microenvironment that supports not only initial adhesion but also subsequent cell growth and network formation. A similar trend was also observed in the case of fibroblasts. Fibroblasts exhibited uniform attachment and spreading along both the flat

substrate and the MN surfaces (Figure 6f). At higher magnifications, distinct filopodia extensions were observed, indicating active cytoskeletal remodeling and tight adhesion to the MN surface. Cellular responses were further quantified using CCK-8 assays as demonstrated in Figure 6f. The degree of proliferation significantly enhanced in the MN groups compared to flat specimens. This enhancement may be attributed to the increased surface area, which provides favorable microenvironments. Supplementarily, angiogenic ability was further assessed by tube formation assay as demonstrated in Figure S20. Fluorescence microscopy images revealed distinct differences in cellular network organization among the experimental groups. The flat and MN groups exhibited relatively sparse and discontinuous cellular structures, whereas the AMN and BMMN groups displayed progressively enhanced intercellular connectivity and more well-defined cytoskeletal organization. The well-organized polygonal structures and intensified fluorescence signals indicate enhanced cytoskeletal integrity and cellular junction formation [110, 111]. Quantitative analysis further supported these observations. Across all measured parameters, the aDNA incorporated groups showed significantly higher values compared with the aDNA-absent groups. In particular, both AMN and BMMN groups exhibited marked increases in structural integrity-related metrics, while the BMMN group consistently achieved the highest values. The obtained results suggest that released DNA substantially enhances cellular performance and non-cytotoxicity of released Zn ion from BMMN. The enhanced structural organization observed in the AMN and BMMN groups may be attributed to its improved antioxidative capacity, as demonstrated in previous ROS scavenging assays since reduced oxidative damage may facilitate extracellular matrix deposition and support angiogenic signaling, contributing to improved tissue regeneration [112, 113].

After aDNA immobilization and Zn S-PIII treatment, further enhancement in proliferation was observed due to the released DNA and Zn ion which promotes cellular responses on the MN surface. The antibacterial activity of Zn ions can suppress bacterial infection and the associated inflammatory responses that may occur during the early stage of tissue regeneration. In addition, the enhanced mechanical properties of the MN, resulting from the Zn nanolayer, effectively support stable cell adhesion following BMMN implantation. Subsequently, DNA is continuously released from the BMMN, exerting ROS-scavenging effects and promoting the proliferation of vascular endothelial cells and fibroblasts, thereby facilitating normal wound healing. These coordinated mechanisms closely reflect the functional characteristics of *Drosera capensis*, which inspired the design concept of this study.

2.9 | Chronic Wound Healing Ability of Biomimetic MNs

The in vivo penetration test confirmed that the MN array successfully pierced the skin surface without noticeable structural damage to the surrounding tissue (Figure 7a). After removal, the puncture sites remained visible but showed no significant tearing or excessive bleeding, demonstrating the minimally invasive nature of the device. Histological analysis further validated the penetration depth and localized tissue disruption. Hematoxylin and eosin (H&E) staining revealed that the MNs consistently

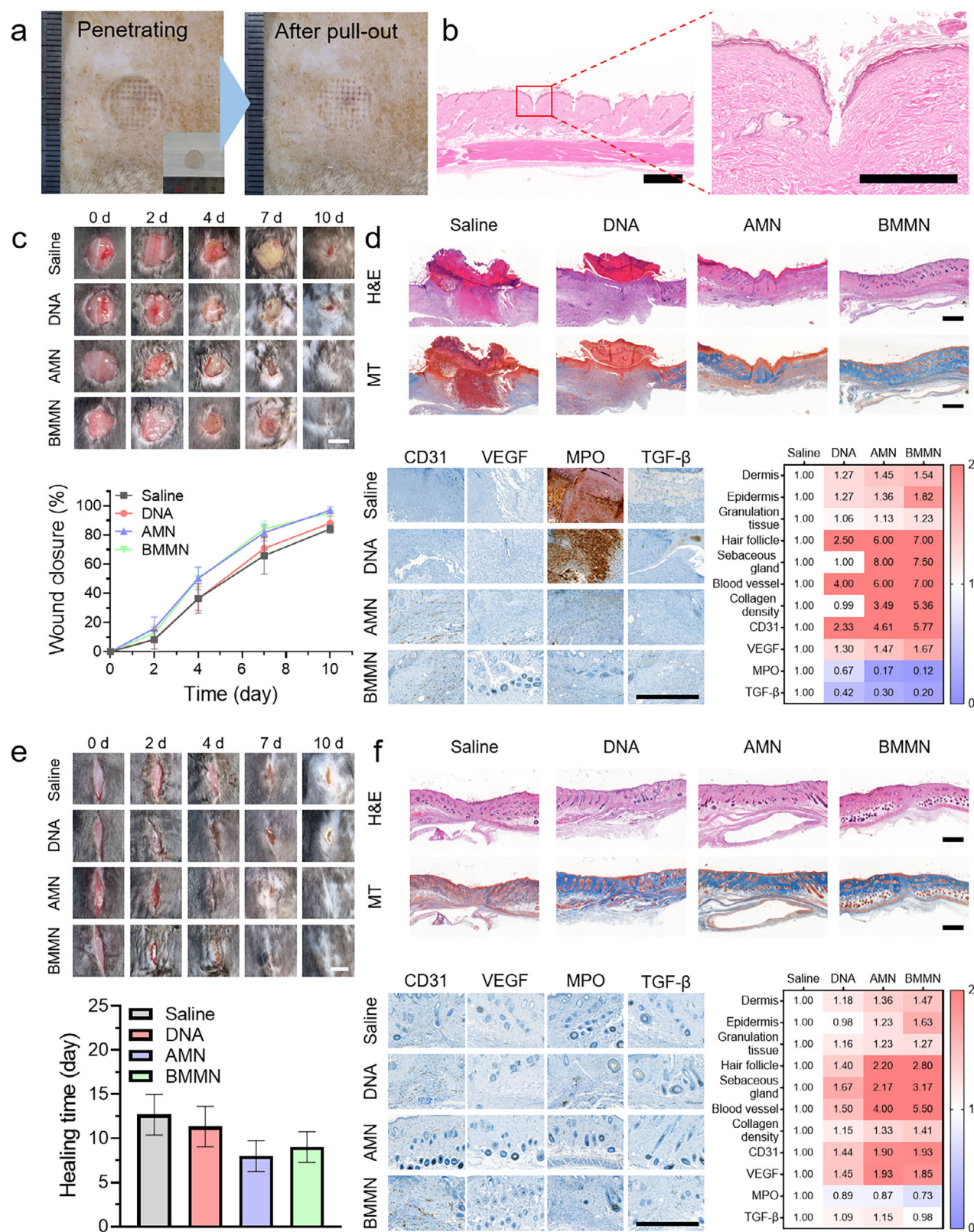


FIGURE 7 | Assessment of diabetic wound healing ability of biomimetic MNs. (a) Optical image after MN application and MN removal. (b) Histological image of MN applied mouse skin with different magnification (scale bar: 500 μ m). (c) Representative optical images of the diabetic normal wound site at a determined time (scale bar: 5 mm) and calculated wound closure. (d) H&E, MT, and IHC-stained images of extracted tissues after 10 days of observation ($N = 4$, scale bar: 500 μ m) and a heatmap of tissue regeneration-related factors with comparison to the saline injection group. (e) Typical optical images of diabetic incisional wound site until 10 days of follow-up period ($N = 4$, scale bar: 5 mm) and assessed healing time for fully recovery. (f) H&E, MT, and IHC-stained images of extracted tissues after 10 days of observation (scale bar: 500 μ m) and a heatmap of tissue regeneration-related factors with comparison to the saline injection group.

breached the stratum corneum and epidermis while maintaining dermal integrity (Figure 7b). Higher magnification images confirmed well-defined microchannels with minimal inflammatory infiltration.

In terms of wound diabetic wound healing, diabetic wounds are characterized by delayed re-epithelialization, impaired angiogenesis, and reduced excessive extracellular matrix (ECM) remodeling due to chronic inflammation and oxidative stress [114, 115]. Thus, overall skin tissue regeneration regarding structural and functional features should be evaluated based on histological analyses. The diabetic wound healing ability of MNs was evaluated utilizing a wound closure model created in the back of diabetic mice. Wound closure images collected over a multi-day period with saline injected (noted as saline), DNA injected (noted as DNA), AMN-treated, and BMMN-treated groups as demonstrated in Figure 7c and Figure S23. Optical images of the wound site demonstrated accelerated healing in MN-treated groups compared to saline (Figure 7c). The wound size reduction was more pronounced after day 5, with nearly complete re-epithelialization observed by day 10. This accelerated healing can be attributed to the combination of microchannel-induced tissue remodeling and enhanced delivery of DNA and Zn ion [12, 14, 116]. H&E and Masson's trichrome (MT) staining (Figure 7d; Figures S24 and S25) revealed enhanced tissue remodeling and collagen deposition with more organized extracellular matrix formation in the treated groups. Reactivation of keratinocyte migration and fibroblast proliferation induced increased dermal and epidermal thickness in the BMMN group. In addition, thicker granulation tissues were observed in aDNA immobilized groups, which reveals an accelerated proliferation phase during wound healing [117, 118]. More dramatic changes were monitored in the density of hair follicles, sebaceous glands, and blood vessels (Figure 7d). Especially for aDNA immobilized MNs, relative values of the above-mentioned factors are larger than 6, which means a sixfold increase compared to saline injection, and it is highly correlated with the function of released DNA. The newly formed collagen fibers exhibited dense and aligned structures compared to the disorganized network observed in saline and DNA-injected groups. Immunohistochemical staining for key markers of angiogenesis and inflammation further confirmed the regenerative effects (Figure 7d; Figure S26). Increased expression of cluster of differentiation 31 (CD31) and vascular endothelial growth factor (VEGF) was observed in the MN-treated wounds, indicating both accelerated cellular proliferation and angiogenic responses. CD31 is a transmembrane glycoprotein predominantly expressed on endothelial cells and is commonly employed as a reliable marker of neovascularization [119, 120]. An increase in CD31-positive staining area reflects enhanced endothelial cell proliferation, migration, and capillary formation. In regenerating tissues, elevated CD31 expression signifies active angiogenic remodeling and the development of functional microvascular networks. These newly formed vascular structures play a critical role in supplying oxygen and nutrients, facilitating waste clearance, and supporting the recruitment of progenitor cells necessary for tissue repair. VEGF is a key pro-angiogenic cytokine that governs endothelial cell survival, proliferation, and vascular permeability [121]. Upon binding to VEGFR-2 on endothelial cells, VEGF activates downstream signaling cascades, including the PI3K/Akt and MAPK/ERK pathways, thereby promoting angiogenic sprouting and vascular maturation. Elevated VEGF

expression typically precedes the formation of CD31-positive vessels, suggesting that VEGF-driven signaling enhances microvascular density in regenerating tissues. Mechanistically, increased VEGF levels establish a pro-angiogenic microenvironment that facilitates endothelial cell chemotaxis and lumen formation. The resulting expansion of CD31-positive microvessels contributes to sustained tissue remodeling by improving perfusion and metabolic exchange. Collectively, the upregulation of VEGF and CD31 reflects an active angiogenic phase that supports accelerated tissue regeneration.

On the contrary, MN-treated wounds showed a decreased degree of inflammation which was measured by the intensity of myeloperoxidase (MPO) and transforming growth factor beta (TGF- β). MPO is predominantly expressed in neutrophils and serves as a marker of acute inflammatory infiltration [122]. MPO mediates the generation of ROS, which play a crucial role in microbial defense but can also cause oxidative tissue damage when produced in excess. Therefore, reduced MPO expression indicates diminished neutrophil recruitment and a mitigated acute inflammatory response. This attenuation of inflammation helps minimize secondary tissue injury and fosters a more favorable microenvironment for tissue regeneration. is a multifunctional cytokine that plays critical roles in inflammation, immune regulation, and fibrosis [14]. Although transient activation of TGF- β signaling is essential for normal wound healing, sustained or excessive stimulation can drive fibroblast-to-myofibroblast differentiation, ECM deposition, and fibrotic scar formation. Therefore, downregulation of TGF- β during the later stages of regeneration suggests attenuation of profibrotic signaling and a transition from inflammation-driven repair to constructive tissue remodeling. In parallel, decreased MPO expression reflects reduced oxidative stress and diminished inflammatory cell-mediated tissue damage. Controlled suppression of TGF- β signaling further limits excessive ECM accumulation and fibrosis, thereby facilitating organized tissue reconstruction rather than scar formation. Collectively, the concurrent reduction of MPO and TGF- β indicates resolution of the inflammatory phase and progression toward a regenerative remodeling phase. The quantitative analysis demonstrated statistically significant increases in these markers compared to the saline injection group, supporting the hypothesis that MN treatment stimulates wound healing through synergistic cellular and vascular mechanisms (Figure 7d; Figure S26).

Macroscopic observation of incisional wound closure in diabetic mice demonstrated significant differences between the experimental and saline-injected groups (Figure 7e,f). The saline-injected diabetic wounds exhibited delayed closure and incomplete scab formation even at later time points. In contrast, wounds treated with the MNs showed accelerated closure with reduced scar formation, indicating enhanced healing efficacy under hyperglycemic conditions. Resulting from the assistance of MN with DNA and Zn, the healing time of the wounds was decreased as illustrated in Figure 7e and Figure S27. Histological analysis with H&E staining revealed marked differences in skin tissue regeneration (Figure 7f; Figure S28). Saline-injected wounds showed incomplete epithelialization with disrupted epidermal layers and persistent inflammatory infiltration. In contrast, MN-treated wounds demonstrated continuous re-epithelialization, neo-vascularization, restoration of skin appendages, and reduced

inflammatory cell presence. MT staining further revealed that collagen deposition in the treated wounds was denser and more organized, while the saline-treated group exhibited sparse and disorganized collagen bundles (Figure 7f; Figure S29). Immunohistochemical analysis provided deeper insights into the molecular mechanisms underlying the observed healing improvements (Figure 7f). CD31 and VEGF staining revealed significantly higher angiogenesis in the MN-treated groups compared to saline and DNA-injected groups [123, 124]. Quantitative analysis confirmed that angiogenic markers were upregulated in the treated wounds (Figure 7f; Figure S30). The intensity of MPO was slightly decreased at MN-treated groups, and the intensity of TGF- β was comparable among the experimental groups when the results are compared to normal diabetic wounds [14, 125]. This was due to decreased wound area from the incisional wound model which is less than 20%. The obtained results demonstrate that the applied MNs with DNA and Zn effectively restored wound healing capacity in a diabetic model by enhancing skin tissue regeneration, promoting collagen remodeling, stimulating angiogenesis, and suppressing inflammation. Although promising results were achieved with BMMN resembling the functionality of *Drosera capensis*, several limitations should be acknowledged for future investigation. The number of experimentally acquired data points for AI modeling was initially limited, which may restrict model robustness. In addition, the temperature evaluation was confined to RT and 37°C, and responses across a wider temperature range were not assessed. Nevertheless, these two temperatures represent the most clinically relevant conditions, and thus, this limitation is unlikely to substantially affect translational applicability. Finally, the developed MNs are not intrinsically biodegradable, which remains an important consideration for future platform optimization.

3 | Conclusions

This study established a data-driven framework integrating correlation analysis and ML modeling to elucidate the shape recovery behavior of 4D-printed MNs under different temperature conditions. The integration of in silico ML-based prediction with in vitro–in vivo tissue validation revealed that thermo-responsive MNs not only restored angiogenic and fibroblastic activity but also reinstated skin integrity and appendage regeneration. Histological analyses demonstrated significant increases in dermal, epidermal, and granulation-tissue thickness, collagen density, and vascular formation, whereas inflammatory infiltration was markedly reduced. The synergistic effects of aDNA-mediated angiogenesis and Zn-induced antibacterial activity achieved rapid wound closure and structurally organized collagen remodeling, yielding tissue architecture comparable to that of healthy skin. Beyond diabetic repair, the demonstrated Gaussian process regression framework enables predictive control of shape-memory polymer behavior, supporting future biofabrication strategies for dynamic biomedical devices. These findings establish the *Drosera capensis*-inspired BMMNs as a clinically translatable, multimodal therapeutic system capable of intelligent shape recovery, controlled biomolecule delivery, and infection-resistant skin regeneration. And the developed SMP system can be extended beyond MNs to applications such as bone scaffolds and stents, enabling shape recovery to match defects and potentially accelerate regeneration.

4 | Experimental Section

4.1 | Materials

tBA, HDDA, antibiotic–antimycotic (AA), glutaraldehyde, 1,1,1,3,3,3-hexamethyldisilazane, Tris-HCl buffer (pH 8.5), dopamine hydrochloride, FITC-albumin, Fluorimetric Hydrogen Peroxide Assay Kit, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), and potassium persulfate, 10% neutral-buffered formalin (NBF), eosin Y solution, nicotinamide (NA), streptozotocin (STZ), citrate buffer (0.09 M), sodium chloride (NaCl) were purchased from Sigma-Aldrich (USA). Omnirad 819 was purchased from IGM Resins (Netherlands). Fetal bovine serum (FBS) was purchased from Gibco (USA). Polydeoxyribonucleotide (PDRN DNA) was obtained from Genoss (Korea). Hydrochloric acid (HCl) and ethanol (EtOH) were purchased from Dae-Jung (Korea). PBS and α -minimal essential medium (α -MEM) were purchased from Welgene (Korea). The D-Plus CCK cell viability kit was obtained from Dongin-LS (Korea). Endothelial growth medium-2 (EGM-2), and agarose gel (SeaKem LE Agarose) were purchased from Lonza (Switzerland). Matrigel growth factor reduced (GFR) basement membrane matrix (LDEV-free) was obtained from Corning (USA). Luria–Bertani (LB) broth and LB agar plates were purchased from BD Difco (USA). Isoflurane (Isotroy) was purchased from Troikaa Pharmaceuticals Ltd. (India). Cefazolin was purchased from ChongKunDang (Korea). Meloxicam was purchased from Boehringer Ingelheim Vetmedica GmbH (Germany). Mayer's modified hematoxylin, MT stain kit, anti-CD31, anti-VEGF Receptor 1 antibody, anti-TGF- β antibody, and anti-MPO antibody were purchased from Abcam (UK). A rodent diet with 60 kcal% fat was sourced from Research Diets Inc. (USA).

4.2 | Synthesis of SMPs

tBA and HDDA were employed as the monomer and crosslinker, respectively, for the fabrication of SMPs. Considering the light wavelength (385 nm) of the equipment (Asiga PICO2 HD, Asiga, AUS), Omnirad 819 was utilized as a radical photoinitiator to induce photopolymerization. Upon UV exposure, polymerization between tBA and HDDA occurs, resulting in the formation of a tBA-HDDA-based SMP (Figure 1a). The influence of crosslinker content to characteristics of SMPs was investigated using solutions containing 10, 30, and 50 wt.% of HDDA. Each formulation included 1 wt.% of Omnirad 819. Solutions containing tBA, HDDA, and Omnirad 819 were homogeneously mixed by 5 min of vortex. After solutions were poured into the var for 4D printing, the printing process was followed under the intensity of UV light was maintained at 18 mW/cm² with a fixed layer thickness of 100 μ m. The exposure time for photopolymerization was varied at 2, 4, 6, 8, 10, and 12 s.

4.3 | Characterization of SMP

Printability assessment was carried out by comparing the dimensional error between the rectangular design (10 $\times$ 2 $\times$ 1 mm³) and printed specimens ($N = 3$). And the experimental conditions that showed an error larger than 20% were regarded as over-curing and

excluded in further experiments. For the tensile test, the design of the specimen followed ISO-527-2 Type 5B, which is widely utilized for examining tensile properties of polymeric materials ($N = 3$). A cubic design with dimensions of $8 \times 8 \times 8 \text{ mm}^3$ was utilized for the compression test ($N = 3$). Each mechanical experiment was conducted using a universal testing machine (MINOS-005, MTDI, Korea) with 1 mm/min of cross-head speed. The thermal properties of fabricated SMPs were evaluated through TGA and DSC. Five milligrams of the sample was inserted in a thermogravimetric analyzer (TGA2, Mettler-Toledo, Germany) with a heating rate of $10^\circ\text{C}/\text{min}$ from 30°C to 900°C and N_2 gas with a flow rate of 50 mL min^{-1} . Four milligrams of the sample were analyzed using a differential scanning calorimeter (DSC 4000, PerkinElmer, USA) with 20°C to 80°C , $10^\circ\text{C}/\text{min}$ of heating rate, and N_2 gas with a flow rate of 20 mL min^{-1} . Shape recovery behavior of prepared SMPs was verified utilizing a ring design with a diameter of 8 mm and a thickness of 1 mm. After producing the ring-shaped SMPs, the SMPs were rinsed by EtOH and DW to eliminate residual chemicals and dried in the fume hood for 1 day. Ring-shaped specimens were cut and left in the oven at 70°C for 2 min, and softened specimens were flattened by put a weight on them for 5 min at RT. A customized jig was fabricated to fix one side of the plate-shaped specimen, which was then immersed in deionized water maintained at either RT or 37°C (Figure S2). The extent of bending over time was quantified by measuring the angular displacement to evaluate the recovery behavior. TMA was conducted from 20°C to 60°C under an applied load of 0.05 N at a heating rate of $5^\circ\text{C}/\text{min}$ in an Ar atmosphere (TMA Q400, TA Instruments, USA).

4.4 | Machine Learning

ML models were developed to predict the shape recovery behavior ($\Delta\text{Deg.}$) of 3D-printed MNs as a function of processing and temporal parameters. The predictive features were the HDDA concentration (wt.%), curing time (s), and recovery time (s), while the output variable was shaping recovery behavior ($\Delta\text{Deg.}$). Separate models were trained for specimens tested at RT (0–1800 s, 60 s intervals) and 37°C (0–90 s, 10 s intervals) because the time scales and deformation kinetics differed significantly.

Each dataset was randomly divided into training, validation, and test subsets in a 70: 15: 15 ratio using random sampling without stratification. For the SVR and GPR models, input features were standardized based on statistics from the training set, and the same transformation was applied to the validation and test sets. XGB models were trained on the original, unscaled features while maintaining identical data partitions and randomization to ensure methodological consistency. Three nonlinear regression algorithms were implemented using Python (Jupyter, scikit-learn, and XGB). The SVR model employed a radial-basis-function (RBF) kernel, and its key hyperparameters—penalty parameter C , tolerance ϵ , and kernel width γ —were tuned within wide numerical ranges to capture potential nonlinearities. For completeness, linear and polynomial kernels (degrees 2–3) were also examined. The GPR model utilized composite kernels consisting of a constant and white-noise component combined with either a radial-basis or Matern covariance function ($\nu = 1.5$ – 2.5). Kernel hyperparameters were optimized by maximizing the log-marginal likelihood using multiple random restarts to ensure

convergence to a global optimum. For the XGB model, the base learner used a squared-error loss function with the number of boosting rounds ranging from 100 to 200, a maximum tree depth of 4–6, learning rates between 0.1 and 0.2, and subsampling and column sampling ratios between 0.8 and 1. All hyperparameters were tuned against the validation set by minimizing the mean-squared error (MSE), and the configuration yielding the lowest validation error was fixed for final evaluation.

$$K(x_i, x_j) = \exp(-\gamma \|x_i - x_j\|^2)$$

Model performance was assessed on the independent test set using the coefficient of determination (R^2 score), RMSE, MAE, and MSE. Parity plots comparing predicted and experimental values, residual analyses, and histograms of prediction errors were generated for both temperatures. For GPR, predictive uncertainty (σ) was obtained analytically using the posterior variance and visualized as confidence bounds; for SVR and XGB, only deterministic predictions were reported, although XGB plots optionally displayed $\pm 1 \sigma$ error bands derived from residual standard deviation for visualization only. To examine variable influence, permutation-based feature importance was computed for all models on the test set, and for XGB, both built-in and permutation importance were recorded and exported.

Fold cross-validation was used to assess the generalization performance of the trained models. The final SVR, GPR, and XGB models trained at both RT and 37°C were subsequently tested on additional datasets with new HDDA concentration (5 and 20 wt.%) and curing time to evaluate generalization performance. Model predictions were compared with experimental measurements to assess their accuracy and robustness, and all analyses were conducted under consistent preprocessing and evaluation conditions to ensure reproducibility.

4.5 | In Vitro Cytotoxicity Evaluation of SMP With 10 wt.% HDDA

To evaluate the cytotoxicity of the fabricated SMP, fibroblasts (NIH3T3, ATCC, USA) and HUVECs (Lonza, Switzerland), which play a critical role in skin tissue regeneration, were utilized. Cell adhesion and proliferation were assessed using FESEM (S-4800, HITACHI, Japan) observations and the CCK-8 assay, respectively. For cell culture, NIH3T3 cells were maintained in α -MEM supplemented with 10% FBS and 1% AA, whereas HUVECs were cultured in EGM-2.

Prior to cell experiments, SMP specimens were prepared in dimensions of $10 \times 10 \times 2 \text{ mm}^3$, sterilized by immersion in 70% ethanol for 30 min, followed by UV irradiation for an additional 30 min. For the cell adhesion study, cells were seeded onto the specimens at a density of 3×10^4 cells/mL. After 24 h, the samples were subjected to post-treatment for FESEM observation. Specifically, the culture medium was removed, and the samples were rinsed twice with PBS. Subsequently, they were fixed in 2.5% glutaraldehyde for 10 min, dehydrated sequentially in 75%, 95%, and 100% ethanol (5 min each), and then immersed twice in 1,1,1,3,3,3-hexamethyldisilazane for 10 min. After platinum (Pt) coating, FESEM imaging was performed. Cell proliferation was assessed using a CCK-8 assay. Briefly, sterilized specimens were

seeded with cells at a density of 2×10^4 cells/mL. At days 3 and 5, the culture medium was removed, and non-adherent cells were eliminated by rinsing twice with PBS. The rinsed specimens were then incubated in culture medium containing 10 v/v% CCK-8 solution for 2 h. The absorbance of the reacted solution was subsequently measured at 450 nm.

4.6 | Fabrication of *Drosera Capensis*-Inspired Thermo-Responsive Microneedles

A two-step DLP 3D printing process was employed to fabricate microneedles in a patch configuration. First, a supporting base was printed at a light intensity of 18 mW/cm^2 , with a layer thickness of $100 \mu\text{m}$ and an exposure time of 8 s, to produce a disc-shaped structure with a diameter of 10 mm and a height of 2 mm. The microneedles were designed in a conical geometry with a height of 1.5 mm and a base diameter of $500 \mu\text{m}$. Beginning from the uppermost $100 \mu\text{m}$ layer, the needle portion was printed under the same light intensity (18 mW/cm^2), but with a reduced layer thickness of $10 \mu\text{m}$ and an exposure time of 6 s. Initially, needles were printed with varying degrees of curvature, and the final patch employed the design with the greatest curvature.

4.7 | Characterization of *Drosera capensis*-Inspired Thermo-Responsive Microneedles

To evaluate the shape recovery ability of the microneedles, the microneedle patch was first placed in an oven at 70°C for 2 min and subsequently cooled to RT. The needle tips were then manually straightened using forceps. The specimens were immersed in deionized water maintained at either RT or 37°C , and the shape recovery process was recorded using a mobile camera.

For the weight-lifting test, microneedles were redesigned by enlarging their diameter and height by 10-fold, resulting in a total volume increase of 1000-fold. The supporting base was designed with dimensions of $10 \times 10 \times 5 \text{ mm}^3$ to allow fixation with a clip. Similar to the shape recovery test, curved needles were straightened under the same conditions, and weights were attached to the needle tips using a thread. The microneedles were heated with a heat gun while the displacement of the weights was recorded using a mobile camera. The applied weights were 10, 20, 30, 40, and 50 g.

4.8 | Preparation and Characterization of aDNA

A 10 mM Tris-HCl buffer was prepared, and dopamine hydrochloride was added at a final concentration of 2 mg/mL. After 2 h of reaction, the resulting PDA solution was mixed with a 2 mg/mL DNA solution at a 1:1 ratio and stirred for 24 h to obtain aDNA nanocomplexes. The morphology and elemental composition of PDA nanoparticles and aDNA were characterized by cryo-TEM (JEM-2100F, JEOL, Japan) equipped with EDS. Holey carbon grids (Quantifoil R 1.2/1.3, 200 mesh Cu, Structure Probe Inc., USA) were glow-discharged at 15 mA for 60 s to enhance sample adsorption. Using a Vitrobot Mark IV (Thermo Fisher, USA) operated at 15°C and 100% relative humidity, $3 \mu\text{L}$ of each sample

was applied to the grids, blotted for 4 s with a blotting force of 1, and immediately plunge-frozen in liquid ethane. The vitrified grids were subsequently transferred to a cryo-transfer holder (Model 626, Gatan, USA) maintained at -180°C and imaged on a transmission electron microscope (JEM-2100F, JEOL, Japan) operated at an accelerating voltage of 200 kV. The size distribution and zeta potential of DNA, PDA, and aDNA were further analyzed using DLS (Zetasizer Nano ZS, Malvern Instruments Ltd., UK).

4.9 | Zinc (Zn) Nanolayer Formation and Characterization

A Zn nanolayer was formed through applying Zn S-PIII to MN patches [94]. The direct current magnetron sputtering system (Ultech Co., Ltd., Korea) was equipped with a Zn target (75 mm in diameter, 5 mm in thickness). For the S-PIII procedure, the Zn target was positioned in parallel with the MN patches, which were secured onto a stainless-steel substrate. The chamber was subsequently evacuated to a base pressure of $5 \times 10^{-4} \text{ Pa}$ using a combination of rotary and diffusion pumps. Plasma treatment was carried out by applying a negative bias of 2000 V for 10 s under an argon atmosphere at 7 mTorr. During the process, a discharge current of 50 mA was maintained without external heating.

The Zn nanolayer was characterized using focused ion beam-transmission electron microscopy coupled with EDS (FIB-TEM-EDS). Prior to imaging, the surface was coated with carbon and Pt, and cross-sectional structures were examined via FIB-TEM. Elemental distribution was further analyzed using line-scan EDS. Surface roughness and near-surface chemical composition were evaluated by AFM (XE-100, Park Systems, Korea) and XPS (ESCALAB 250Xi, Thermo Fisher Scientific Inc. USA), respectively.

The mechanical properties resulting from the Zn nanolayer deposition were assessed through surface hardness measurements and compression testing of the microneedles. Nanoindentation was performed using a nanoindenter (Picodentor HM500, Helmut Fischer, Germany) with a Berkovich-type diamond tip under load control mode. A maximum load of 20 mN was applied ($N = 3$). After indentation, surface structures were observed using laser scanning microscopy (OLS 4100, Olympus, Japan) and FESEM (Apero2S, Thermo Fisher Scientific Inc., USA). Straight microneedles were subjected to compressive loading while monitoring deformation using a universal testing machine (MINOS-005, MTDI, Korea) at a strain rate of 1 mm/min.

4.10 | Examination of Antibacterial Property

The antibacterial activity of the microneedle patches was evaluated using a colony-forming assay with the gram-negative bacterium *E. coli* (ATCC 8739, Rockville, MD, USA) and the gram-positive bacterium *S. aureus* (ATCC 6538, Rockville, MD, USA). Each bacterial strain was pre-cultured by inoculating $50 \mu\text{L}$ of the stock solution into 3 mL of Luria-Bertani (LB) broth and incubating for 18 h. Microneedle patches, including the needles and the supporting base (8 mm diameter, 2 mm height), were sterilized via UV irradiation and affixed to the wells of a culture plate using carbon tape. Subsequently, $30 \mu\text{L}$ of bacterial

suspension (1×10^4 CFU/mL for *E. coli* and 1×10^8 CFU/mL for *S. aureus*) was applied onto the patches and incubated at 37°C for 3 h with shaking at 200 rpm (SI-300R, Lab Companion, USA). Following incubation, specimens were rinsed with PBS and transferred into 3 mL of fresh LB broth. Adherent bacteria were dislodged by vortexing for 1 min, and 100 μ L of a 1:100 dilution of the bacterial suspension was spread onto LB agar plates. The resulting colonies were enumerated after 24 h of incubation at 37°C under humidified conditions. Colony counts were quantified from digital images, and the average values were reported.

4.11 | Biomolecule/aDNA Immobilization and Biocompatibility Assessment

The biomolecule loading capacity of the MNs was evaluated using FITC-albumin. A 1 mg/mL FITC-albumin solution was prepared, and PMNs were immersed in the solution and incubated under stirring at 80 rpm for 24 h. After incubation, unbound FITC-albumin was removed by washing twice with PBS, and the MNs were air-dried at RT for 24 h. To assess penetration, 1% agarose gel was prepared. MNs with and without FITC-albumin were inserted into the gel and subsequently withdrawn. The morphology immediately after penetration and the distribution of FITC-albumin in the gel were examined using optical microscopy and fluorescence imaging (ECLIPS Ti2, Nikon, Japan).

For DNA release studies, aDNA was loaded onto MNs, followed by washing and drying, after which Zn S-PIII treatment was applied. The MNs were then immersed in 2 mL of PBS, and at predetermined time points, aliquots were collected to measure absorbance at 258 nm using a UV-Vis spectrophotometer (NanoDrop 2000c, Thermo Scientific, USA). Relative release profiles were quantified using a standard curve and normalized to the total loaded DNA ($N = 3$). Cellular responses to MNs under different treatment conditions were evaluated as previously described ($N = 3$). A tube formation assay was performed using HUVECs. Matrigel was diluted 1:1 (v/v) with EGM-2, and 100 μ L of the diluted Matrigel was added to each well of a 24-well plate. The plate was then incubated at 37°C for 24 h to allow complete gelation. Subsequently, HUVECs were seeded onto the solidified Matrigel at a density of 3×10^4 cells per well and cultured at 37°C for an additional 24 h. After 24 h incubation, EGM-2 was refreshed by extracted medium with MNs and cultured for an additional 24 h. Subsequently, the cells were stained with a calcein AM solution and visualized using inverted fluorescence microscope (ECLIPS Ti2, Nikon, Japan). Quantitative analysis of tube formation, including angiogenic parameters, was performed using the Angiogenesis Analyzer plugin in ImageJ software. Additionally, the hydrophilicity of MNs following aDNA loading and Zn S-PIII treatment was assessed using the sessile-drop method with distilled water ($N = 3$).

4.12 | Fluorometric Hydrogen Peroxide Assay

Hydrogen peroxide scavenging activity was evaluated using a fluorometric hydrogen peroxide assay kit. Prior to conducting

the assay, the extraction medium was prepared by immersing each specimen in 1 mL of culture medium. Fifty microliters of a 50 μ M H₂O₂ stock solution was mixed with 50 μ L of each extracted solution and incubated for 15 min under dark conditions with gentle shaking. The fluorescence intensity was then measured using a microplate reader (Synergy H1 Hybrid Multi-Mode Reader, BioTek, USA) at an excitation wavelength of 540 nm and an emission wavelength of 590 nm.

4.13 | ABTS Inhibition Assay

ABTS radical scavenging activity was assessed by mixing 950 μ L of ABTS solution with 50 μ L of each extracted solution in 1 mL tubes, followed by incubation for 10 min under light-protected conditions with shaking. After centrifugation, 200 μ L of the supernatant was transferred to a 96-well plate, and the absorbance was measured at 732 nm using a microplate reader (Synergy H1 Hybrid Multi-Mode Reader, BioTek, USA).

4.14 | In Vivo Evaluation of Biomimetic Microneedle Patches

In vivo evaluations from animal selection to sacrificial policies were approved by the Institutional Animal Care and Use Committee of the Catholic University of Korea (CUK-IACUC-2022-010). C57BL/6 mice with the age of 6 weeks (body weight g) were obtained from Oritentbio (Korea), and the mice were housed in a regulated condition consisting of 20°C–23°C temperature range, 40%–60% of humidity range, and a 12 h light/dark cycle.

The penetration ability of microneedles was evaluated by applying microneedles to the skin of rats. After shaving the dorsal hair of the rat skin, microneedle patches were applied. Penetrated skin by microneedles was fixed by 10% NBF and subsequently embedded in paraffin for H&E staining. For preparing a type 2 diabetes-induced mouse model, fasting was kept up for 16 h prior to introducing drugs to cause diabetes. NA (240 mg/kg) was given 15 min before STZ was administered. STZ (100 mg/kg) was given twice, on days 0 and 2, after being dissolved in a buffer containing 50×10^{-3} M citric acid. Additionally, type 2 diabetes and obesity were created by giving them a 60% fat diet for three weeks. On days 0, 2, and 7 after the induction of diabetes, blood was drawn from a mouse's tail vein. Using a blood glucose test meter (Accu-Chek Active Set, Sanmina Ltd., China), plasma glucose concentration was assessed 16 h after the removal of food. After the plasma glucose content was measured, mice were immediately given food. Diabetes was considered to have been induced when fasting blood glucose was 200–300 mg/dL after a week of a combination of drugs and high-fat diets. The dorsal hairs of the diabetic mice were shaved, and the region was disinfected with povidone-iodine and alcohol. Prior to generating wound, mice were anesthetized with 1.5%–3% isoflurane. Subsequently, two full-thickness wounds were made on the dorsal skin of mice using a sterile 6 mm punch biopsy tool (Kai sterile dermal biopsy punch, Kai Medical, Japan).

And two incisional wounds were created at the back of diabetic mice using a surgical blade. Succeedingly, saline (0.9% NaCl),

2 mg/mL DNA solution, AMN, and BMMN were applied on top of the wound site. To avoid the undesired detachment of microneedle patches, Tegaderm-film (3 M, USA) was applied to the wounds, and the mice were redistributed at a density of three animals per cage. In addition, 20 mg/kg of cefazolin and 1 mg/kg meloxicam were administered during 3 days of follow-up period. Morphology of the wounds was monitored at a determined time point, and the degree of wound closure was calculated by the equation suggested below;

$$\text{Wound closure (\%)} = \left(\frac{A_0 - A_t}{A_0} \right) \times 100$$

where A_0 : Original wound area (at day 0) and A_t : Remaining wound area (at day t).

4.15 | Histological Evaluation

Skin tissues were extracted at day 10 and fixed for 10% NBF and them embedded in paraffin. H&E and MT stains were used in accordance with the manufacturer's instructions to stain the paraffin-embedded sections of 4 μ m thick samples. Using an optical microscope (Olympus BX53 microscope, Olympus Corporation, Japan), three microscopic fields were taken to measure the cellularity of the H&E-stained picture and the collagen density of the MT-stained image. On 3 mm paraffin slices of the wound skin samples, immunohistochemical (IHC) examination was carried out. Using ethyl alcohol with a concentration ranging from 100% to 70%, a deparaffinized sectioned slide was hydrated. After washing in tap water, antigen retrieval is done using the slide that has undergone hydration for 45 min at 90°C. Use a citrate buffer solution of 0.1×10^{-3} M (pH 6.0). Using the ImageJ program from the National Institutes of Health, the optical density of CD31, VEGF, MPO, and TGF- β expression was calculated.

4.16 | Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 26 (IBM, USA), and the data are represented as mean $\pm$ standard deviation. The one-way analysis of variance (ANOVA) with Tukey's post hoc and Kruskal–Wallis H -test with a pairwise comparison were used to determine whether differences were significant. Tables S2–S21 in the Supporting Information list results of statistical analyses.

Author Contributions

H.L. and M.K. wrote and edited the manuscript throughout all of the activities. H.J. edited the manuscript. M.K., D.K., J.J., J.S., and M.L. carried out ML-based modeling. C.M., S.B., H.K., Y.J., and Y.E. assessed physiological evaluations. J.G. and J.S. examined in vitro cellular responses. M.K. conducted cryo-TEM analyses. D.L., D.L., G.C., and S.L. contributed to the explanation of in vitro tests. J.P. and K.Y. contributed to the understanding of animal results. T.S. contributed to the verification of nanostructures. H.L., M.K., and H.J. contributed to the interpretation and discussion of the results.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. RS-2024-00405381; RS-2025-00513935); and the Korea Institute of Marine Science & Technology Promotion (KIMST) funded by the Ministry of Oceans and Fisheries (RS-2024-00405273); and Korean Fund for Regenerative Medicine (KFRM) grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Health & Welfare, KFRM 24A0105L1); and Korea Institute of Industrial Technology (KITECH) (KITECH UR-26-0018 and KITECH UR-25-0112). M.K. and D.K. were supported by the Korea Institute of Industrial Technology (KITECH)(KITECH EH-26-0002); and the Korea Evaluation Institute of Industrial Technology (KEIT), funded by the Ministry of Trade, Industry and Energy (MOTIE) (Grant No.RS-2024-00410959).

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting file 1: adma72932-sup-0001-SuppMat.docx **Supporting file 2:** adma72932-sup-0002-MovieS1.mp4.