

REVIEW

Electric Field-Empowered Nanozymes: From Passive Adaptation to Active Precision Therapy

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Received: 6 March 2026 | **Revised:** 23 May 2026 | **Accepted:** 23 June 2026

Keywords: electric field regulation | nanozymes | precision therapy

ABSTRACT

The clinical translation of nanozymes is hindered by the passive and uncontrollable catalytic properties, necessitating active and precise spatiotemporal regulation. Inspired by the electrostatic preorganization theory of efficient natural enzymes, this review provides a systematic analysis of electric field-regulated nanozymes. Compared to conventional physical stimuli, this approach offers a tunable and complementary framework for active precise therapy. Diverse electrical input modes provide adaptable driving forces for precisely regulating nanozyme catalysis across various biomedical scenarios. Furthermore, at the atomic scale, the underlying mechanisms are elucidated, demonstrating how the electric field inputs optimize the d-band center, surface charges, band structure, and active sites to promote substrate adsorption and lower reaction energy barriers, thereby enhancing the catalytic effect. To maximize electric field-nanozyme coupling, design principles for a complete charge pathway are distilled: optimizing intrinsic field response, directional charge rectification, and achieving low-loss transport. Subsequently, the applications of electric field-regulated nanozymes in precision therapy are summarized, including on-demand spatiotemporal activation, quantitative dosage regulation, and active microenvironment remodeling. Finally, this review highlights the immense potential of interdisciplinary integration in overcoming the biosafety and mechanism bottlenecks of this regulation strategy. These insights provide a new perspective for advancing electric field-regulated nanozymes toward precision therapy.

1 | Introduction

Nanozymes, nanomaterials with intrinsic enzyme-like catalytic activities, are emerging as robust alternatives to natural enzymes due to their high stability, cost-effectiveness, and rational designability [1]. They have demonstrated great potential in the biomedical field and have been widely applied in tissue repair [2, 3], tumor therapy [4, 5], bacterial inhibition [6], and biosensing [7, 8]. However, current catalytic therapy is undergoing a

paradigm shift from passive response to active precision treatment. The clinical translation of conventional nanozymes is limited by this unpredictable passive mechanism [9–11]. Once nanozymes are introduced into the physiological environment, their catalytic behavior is largely controlled by passive diffusion and local substrate concentration, rendering the performance difficult to regulate [12]. This uncontrolled catalysis may lead to therapeutic failure due to suboptimal activity or damage to healthy tissues arising from excessive catalysis [13, 14]. Therefore,

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it is of great significance to develop dynamic regulation strategies for nanozyme activity to achieve on-demand and precise therapy.

Currently, the strategies for regulating the activity of nanozyme primarily rely on responses to endogenous signals (e.g., pH [15, 16], hypoxia [17], and glutathione [18]) or exogenous physical stimuli (e.g., magnetism [19], photo stimulation [20], and sound stimulation [21]). These strategies have substantially improved the controllability of the catalysis of nanozymes, achieved stimulus-responsive therapeutic functions, and each strategy has its own distinct advantages. Endogenous triggering factors have selectivity for the disease microenvironment [22, 23], for example, light can achieve precise external activation [24], ultrasound has the deep-tissue accessibility [25], and magnetic or thermal regulation provides additional opportunities for remote control and therapeutic integration [26, 27]. However, these strategies still cannot fully meet the requirements of precision therapy such as spatial localization, temporal control, dosage adjustment, mechanistic clarity, and biosafety. Based on these considerations, electric field regulation can be regarded as another important strategy for controlling nanozymes.

This strategy is inspired by the role of electrostatic fields in natural enzymatic catalysis. According to the theory of electrostatic preorganization, the exceptional catalytic efficiency of natural enzymes originates from the precise internal electric field (IEF) generated by the protein scaffold, which preferentially stabilizes the transition state of the reaction [28]. Ferrer et al. demonstrated the critical role of the IEF in enzymatic catalysis through high-level quantum mechanics/molecular mechanics (QM/MM) simulations. The reaction rate was reduced by 10^{35} -fold after removing the charges in the protein and solvent environments [29]. Chaturvedi et al. conducted a systematic study on chorismate mutases (CM) with different structures but similar functions, and clarified the fundamental role of electric fields in the catalytic action [30]. Through the electric fields with remarkably similar orientations and magnitudes, two enzymes with completely different structures can efficiently catalyze the same reaction. This electrostatic similarity underlies their equivalent catalytic efficiency, as evidenced by the strong linear relationship between the reaction rate and electrostatic field. Moreover, by substituting Zn^{2+} with Co^{2+} in liver alcohol dehydrogenase (LADH), Zheng et al. amplified the internal electric field to -174 MV/cm, which led to a remarkable 14-fold increase in the catalytic rate constant [31]. This study established a direct and predictable correlation between the electric field strength at the active site, the reaction energy barrier, and the resulting catalytic kinetics. These findings emphasized that electric fields can effectively enhance and regulate the catalytic activity, providing a fundamental framework for the rational regulation of nanozymes. Although these nanozymes do not possess the IEF generated by the protein scaffold, the external electric fields can actively remodel the catalytic behavior of nanozymes by precisely regulating the intrinsic electronic structures of the nanozymes [32–34].

To date, no review has comprehensively explored the mechanisms related to the regulation of nanozymes by electric fields. Here, we present a detailed discussion in this field, including the input mode of electric fields, the regulation mechanism, therapeutic applications, and material design strategies (Figure 1).

Specifically, we first clarified the unique characteristics and energy generation mechanisms of various electric field sources used for regulating nanozymes. Then, we examined the influence of electric fields on the electronic structures of nanozyme (for example, d-band center, surface charge, active sites, and band structure), and how these effects subsequently impact the catalytic process (substrate adsorption and reaction barrier), thereby revealing the regulatory mechanisms at the atomic scale. Furthermore, we demonstrated how the electric field enables nanozymes to overcome the limitations of conventional therapies, achieving precise, quantitative treatment at both spatial and temporal scales, and facilitating the remodeling of complex pathological microenvironments. In addition, we outlined the material design strategies aimed at strengthening the synergistic coupling between electric fields and nanozymes. Finally, we conducted a thorough analysis of the current challenges and prospects for electric field-regulated nanozymes, highlighted the bottlenecks regarding biosafety trade-offs, mechanistic opacity, and deep-tissue delivery, and proposed future perspectives for interdisciplinary transformation. In summary, this article helps to deepen the understanding of how electric fields regulate nanozymes, and open up new possibilities for the development of the next generation of targeted nanomedicines in precise treatment.

2 | Positioning Electric Fields Among Nanozyme Regulation Strategies

The regulation of nanozymes can be achieved through diverse biochemical and physical strategies. These strategies differ significantly in terms of activation conditions, controllability, tissue accessibility, safety profiles, and their relationships with catalytic reactions. It is necessary to evaluate electric-field regulation within the broader landscape of nanozyme regulation strategies.

Endogenous signals-responsive regulation is one of the most widely used strategies. This response can exploit biochemical differences between pathological and normal tissues, and achieve disease-specific treatment without external devices [35, 36]. Wang et al. developed a pH-responsive nanozyme (CeOSL) for the treatment of multidrug-resistant *Helicobacter pylori* infections and the regulation of inflammation [37]. CeOSL exhibited pH-responsive switchable enzyme activity: under neutral conditions, it displayed reactive oxygen species (ROS)-scavenging ability, while in the acidic stomach environment, it displayed oxidase activity. Qi et al. designed a glucose-responsive cascading nanozyme system (PPCG) that utilizes the abnormally elevated glucose levels in diabetic infected wounds as an endogenous trigger signal. This ensures that the nanozymes are activated only in glucose-enriched infected areas, enabling efficient and selective biofilm removal [38]. This strategy achieves spatially selective regulation of nanozymes. But it is difficult to make adjustments after administration, such as real-time or dose-programmable regulation [39].

To compensate for the limitations of endogenous trigger mechanisms, exogenous physical stimuli have been extensively explored, among which photo-stimulation is a primary approach. Photo-responsive nanozymes combine intrinsic enzymatic activity with external light irradiation to augment catalytic activity and

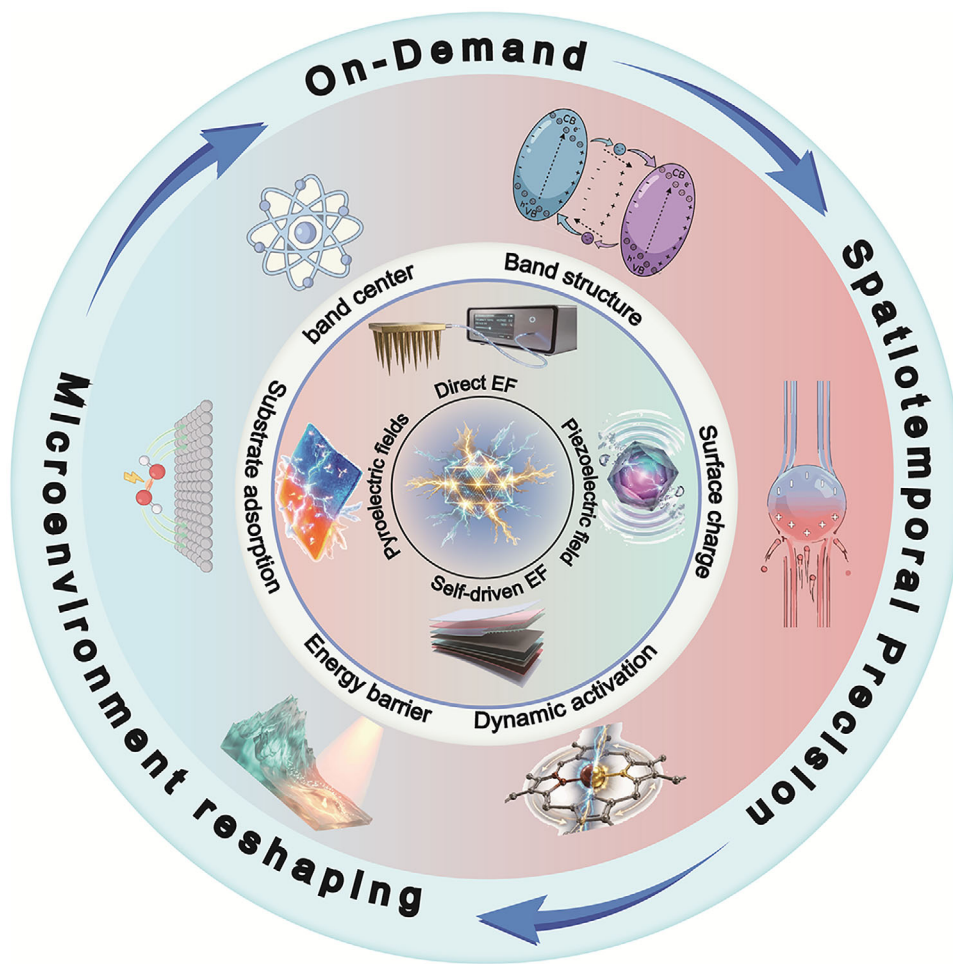


FIGURE 1 | Schematic diagram of electric field-regulated nanozymes.

provide high spatiotemporal selectivity [40]. Under specific light exposure, photon excitation generates electron-hole pairs that subsequently migrate to the nanozyme interface to accelerate the catalysis. Precious metal nanozymes can also utilize the localized surface plasmon resonance (LSPR) effect to concentrate light energy, generating localized hyperthermia and energetic hot carriers, thereby substantially lowering the activation energy barrier of the catalytic reactions [41]. Liu et al. selectively enhanced the peroxidase (POD)-like activity of Au@CeO₂ on a spatiotemporal scale using 808 nm near-infrared light as an external switch, which significantly improved the catalytic activity following irradiation [42]. Mangrio et al. reported a CuS-mediated NIR-photo-regulated nanozyme hydrogel for infected wound healing. The light-induced temperature was tunable by irradiation time, power density, and nanozyme concentration, thereby modulating POD-like activity, ROS generation, H₂O₂ utilization, and GSH depletion. This design converted spatiotemporally controlled light input into adjustable redox therapy output, enabling on-demand antibacterial and wound-healing therapy [43].

However, the regulation of nanozymes by light is limited by tissue penetration depth, phototoxicity, and thermal damage. The significant scattering and absorption of photons by biological tissues restrict the effective penetration depth, rendering this approach unsuitable for deep-seated lesions [44, 45]. More importantly, this strategy relies on light-induced heating to regulate the activity

of nanozyme, which may directly cause nonspecific thermal damage to surrounding healthy tissues [20].

Ultrasound (US)-regulated nanozymes have clear advantages in deep-tissue treatment. Compared to light, US can penetrate tissue more effectively and can be focused in a noninvasive manner [46]. It can enhance the efficacy of nanozyme therapy through various means such as cavitation effect, sonodynamic reactions, mass-transfer enhancement, mechanical effects, or local heating. These features make the US attractive for deep tumors, bacterial infections, and tissue barriers. Bai et al. designed an Nb₂C-Pt@HA-PEG nanozyme that achieves precision therapy of atherosclerosis via ultrasound regulation. It employs exogenous ultrasound to excite internal electron transfer on demand, instantaneously converting its catalytic activity for local ROS scavenging [47]. Li et al. achieved precision therapy for neuroblastoma by spatiotemporally regulating the enzyme-like activity of the COP_{TPeFe} nanozyme using US stimulation. The POD-like activity of COP_{TPeFe} was enhanced to 1.7-fold of its original level. Based on the in vivo accumulation of the nanozyme in tumors (8 and 48 h), US irradiation was applied at these two time points, achieving precise temporal control of the treatment. This US-regulated nanozyme therapy significantly suppressed tumor growth without causing noticeable damage to normal tissues [48]. Nevertheless, US-regulated nanozyme therapy still faces several key limitations. The mechanisms by

which the US activates catalytic reactions remain to be further clarified [49]. Moreover, the biosafety and clinical translatability of sonosensitizers are main concerns. Many conventional organic sonosensitizers originate from photosensitizers, which may lead to severe skin phototoxicity and unfavorable pharmacokinetic profiles, such as poor water solubility and limited tumor-targeting specificity [50].

Magnetic regulation represents another important strategy for nanozyme modulation. The magnetothermal effect of magnetic nanozymes is utilized to regulate their catalytic activity. Under an alternating magnetic field (AMF), magnetic nanozymes generate localized heat at the catalytic surface through Néel/Brown relaxation or hysteresis loss, which accelerates the catalytic process. He et al. demonstrated this principle using iron oxide nanozymes with different specific absorption rates (SARs). The POD-like activity of iron oxide nanoparticles was enhanced in situ under AMF stimulation, and the degree of activity enhancement was positively correlated with both AMF strength and intrinsic SAR [51]. Compared with light-induced temperature elevation, this magnetothermal regulation may reduce the risk of nonspecific thermal damage. Zhang et al. optimized nanozyme cascade kinetics by constructing a series of $\text{Fe}_3\text{O}_4\text{NR@GOx}$ systems with nanometer-scale linking distances. The optimized $\text{Fe}_3\text{O}_4\text{NR}(\text{D}_2)\text{@GOx}$ exhibited over 400-fold higher cascade catalytic activity than the mixture of free GOx and $\text{Fe}_3\text{O}_4\text{NR}$ under AMF exposure [52]. This result further validated the effectiveness of the magnetic-mediated spatiotemporal cascade catalytic regulation. Zheng et al. dynamically control uric acid homeostasis by this strategy to regulate nanozyme for gout treatment. Under AMF control, the NUOx exhibited a switching ratio as high as 7.6 and demonstrated strong reversibility [53]. However, the magnetic field is difficult to focus as precisely as light beams or electrode-defined stimulation. The spatial selectivity of magnetic regulation largely depends on the accumulation of nanozymes at the lesion site. The non-targeted accumulation of nanozymes may also lead to unexpected catalytic activation under magnetic stimulation, increasing the risk of nonspecific oxidative or thermal damage [54].

From the above, it can be seen that each method regulates nanozyme activity through distinct physicochemical pathways and possesses unique advantages. However, conventional physical stimulation methods typically rely on secondary energy conversion. Specifically, they utilize localized photothermal heating, magnetothermal dissipation, or acoustic cavitation to indirectly change reaction kinetics. Compared with the existing strategies, electric field regulation provides a completely new approach for controlling the catalytic reactions of nanozymes. Electric-field regulation represents a paradigm shift by directly modulating the intrinsic electronic structure of the nanozyme at the atomic scale [55]. An applied electric field will force a redistribution of surface charges to emulate the electrostatic pre-organization found in natural enzymes [56]. Consequently, this direct electronic coupling will shift the d-band center, optimize intermediate adsorption energy, and fundamentally lower the thermodynamic activation energy barrier [57]. This feature is particularly important for oxidoreductase-like nanozymes, as their catalytic cycles are intimately associated with electron transfer and intermediate activation. Furthermore, the highly tunability of electrical stimulation enables precise and quantitative control

of the nanozyme activity [58]. To provide a comprehensive and intuitive evaluation of these diverse regulation strategies, a horizontal comparison highlighting their respective advantages and limitations is summarized in Table 1.

3 | Electric Field for Controlling Nanozymes

To fully utilize the regulating effect of the electric field, it is necessary to precisely apply the electric stimulation to the contact interface of the nanozyme. Currently, multiple electrical input modalities have been employed to regulate nanozymes [59]. The specific form of electric field dictates the interaction mechanisms, the efficiency of energy transfer, and the scope of practical applications. This chapter systematically explores the four fundamental electric field sources that drive the activity of nanozyme: direct external electric field, ultrasound-mediated piezoelectric field, pyroelectric fields, and self-powered triboelectric fields (Figure 2). These patterns range from direct wired connections to sophisticated wireless energy collection systems. In order to distinguish the regulatory mechanisms and application scopes of different electric-field inputs, electric field-regulated nanozymes are classified based on the origin and input mode of the electric field. This classification emphasizes the differences in energy sources, material requirements, regulatory parameters, and catalytic pathways among these systems, as summarized in Table 2.

3.1 | Direct External Electric Fields

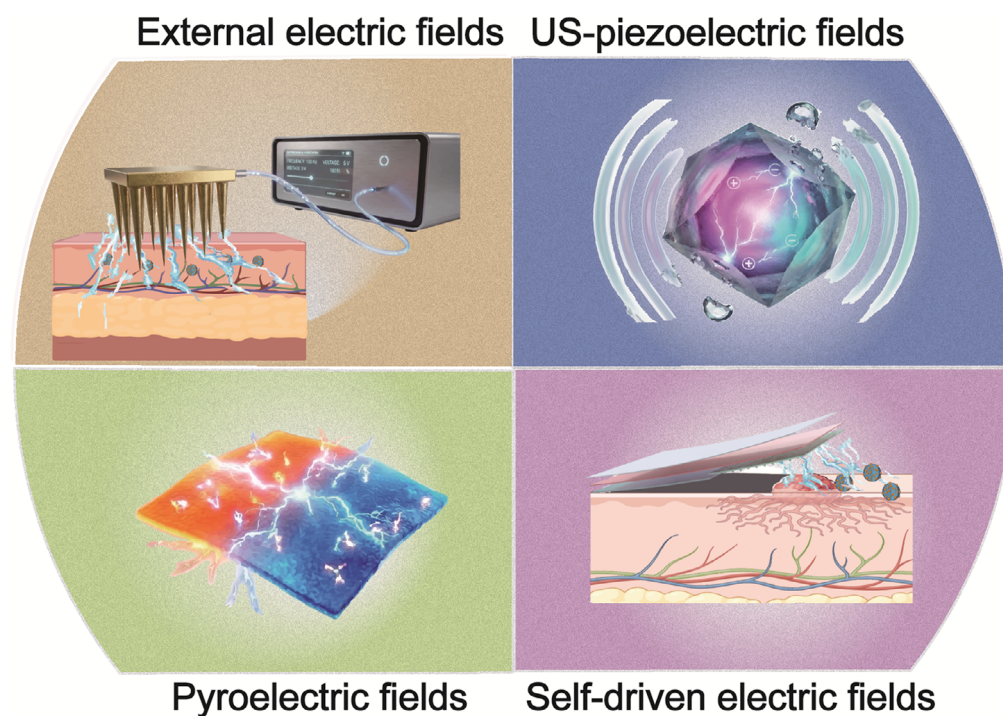
Direct external electric field is the most straightforward regulatory modality. In this approach, the potential difference or current is supplied by external power sources, such as electrochemical workstations, batteries, or implantable microelectrodes [60]. The electrical signals are delivered to the nanozyme system via physically connected electrodes. The paramount advantage of external electric fields lies in the ability to precisely control the operational parameters. Specifically, the strict regulation of variables, including voltage amplitude, current density, and waveform, provides a deterministic input for the thermodynamic driving force of the catalysis [61].

3.1.1 | Direct Current (DC) Electric Fields

DC and alternating current (AC) are the foundational modalities of external electric field input, offering distinct operational mechanisms and application scenarios. By applying a constant potential, DC fields provide a sustained and directional driving force for the catalytic system (Figure 3A) [62]. The catalytic activities of nanozymes can be modulated by manipulating the orientation of DC electric fields. Specifically, Wang et al. applied a positive potential of +0.3 V, which yielded a 343.4-fold enhancement in catalytic efficiency compared to the free state, whereas a -0.3 V negative potential led to significant inhibition of the reaction (Figure 3B) [63]. Furthermore, this modality is highly suitable for driving redox reactions that involve explicit electron transfer pathways. For instance, initiating a reduction reaction by transferring electrons from the electrode to the substrate molecule requires the application of a negative

TABLE 1 | Horizontal comparison of existing nanzyme regulation strategies.

Regulation strategies	Main activation mechanism	Spatiotemporal precision	Quantitative control	Advantages	Limitations
Endogenous biochemical signals	Endogenous stimuli-induced structural disassembly	Low	Low	No external stimuli required	Uncontrollable in vivo pharmacokinetics
Photo regulation	Photothermal conversion, localized surface plasmon resonance, hot electron injection	High	High	Remote activation, high spatial resolution	Limited tissue penetration depth, risk of non-specific thermal damage
Ultrasound regulation	Acoustic cavitation, sonoluminescence, enhanced mass transfer via mechanical shear forces	High	Middle-high	Exceptional deep-tissue penetration	Biosafety threat of sonosensitizer
Magnetic regulation	Magnetothermal effects	Middle	High	Deep-tissue penetration without signal attenuation	Risk of off-target catalysis
Electric field regulation	Direct electronic structure modulation	High	High	Directly controlling the microscopic electronic structure	Requires sophisticated material design

**FIGURE 2** | Schematic illustration of diverse electric field sources for modulating nanozymes.

potential. Leveraging this deterministic driving force, Zou et al. successfully applied a constant negative potential in a dual-electrode system with a gold nanoparticle as the cathode to facilitate the transfer of electrons from the electrode to oxygen molecules. This dual-electron oxygen reduction reaction (ORR) efficiently catalyzed for the selective generation of H_2O_2 as a critical intermediate, enabling indirect control over NO produc-

tion (Figure 3C) [64]. Furthermore, the constant DC supply was also utilized to drive electroosmotic flow within the positively charged porous microneedles, thereby facilitating the migration of dissolved NO toward the skin interface. However, prolonged application of DC stimulation will induce some side reactions, such as electrode polarization, electrolyte decomposition, and drastic local pH fluctuations. These detrimental processes may

TABLE 2 | Classification framework and representative metrics of electric field-regulated nanozymes.

Category	Subtype	Energy source	Material properties	Key regulatory parameters	Catalytic mechanism
Direct external electric fields	DC field	External power source	Electrochemically active	Voltage, current density, electrode distance, polarity	Directional electron Injection/extraction, regulation of the redox state
	AC field			Voltage amplitude, frequency, waveform	Dynamic valence-state cycling, adsorption/desorption modulation
	Pulsed electric field			Pulse amplitude, pulse width, frequency, duty cycle	Local field enhancement, membrane electroporation
Ultrasound-mediated piezoelectric fields	—	External ultrasound	Non-centrosymmetric piezoelectric	US frequency, power density, duty cycle, acoustic pressure, d33	D-band center, surface charge, dynamic activation and regeneration of active sites, band structure
Pyroelectric fields	—		Pyroelectric	Δt , dt/dt, thermal cycling frequency, pyroelectric potential/current	
Self-powered electric fields	—		Piezoelectric, triboelectric, wearable/implantable TENG	Open-circuit voltage, short-circuit current, surface charge density, frequency	

potentially induce tissue necrosis [65]. Thus, the applicability of DC mode is critically limited in long-term implantable scenarios.

3.1.2 | Alternating Current (AC) Electric Fields

Compared to DC electric fields, superior biocompatibility is exhibited in AC fields. By periodically reversing the polarity of electric fields, it is possible to effectively prevent continuous charge accumulation and reduce the associated risk of tissue damage. Crucially, this periodic reversal of the AC field direction can dynamically modulate the active valence states of nanozymes and interfacial dynamic process of adsorption-desorption of substrates and intermediates. Li et al. markedly enhanced the enzymatic activity of PtIrFeMoZn high-entropy alloy (HEA) nanozymes by pre-treatment with square-wave AC field (3.0 V, 10 MHz, 10 min). As an electron pump, AC stimulation propelled the formation and enrichment of highly active metallic species. This process induced a profound electronic redistribution, which concurrently bolstered substrate adsorption and electron transfer efficiency [66]. Tan et al. achieved the coupling of oxidation and reduction reactions on a single electrode using an AC field, thereby facilitating the sequential conversion pathway from H₂O to O₂ and subsequently to H₂O [67]. Simultaneously, the applied electric field caused e⁻ to move toward the electrode surface, enabling the rapid reduction of inactive Ce⁴⁺ to the active Ce³⁺ state (Figure 3D). This electric field-enhanced strategy exhibited potent antitumor efficacy.

3.1.3 | Pulsed Electric Fields

In contrast to continuous DC/AC fields, pulsed electric fields are presented in the form of high-frequency, intermittent bursts with ultra-short durations (~ns/μs) and high instantaneous power (~kV/cm) [68, 69]. Due to this characteristic, significant Joule heating can be avoided, therefore protecting adjacent healthy tissues from thermal injury. Pulsed electric fields can efficiently induce electroporation in cell membranes, significantly augmenting membrane permeability of nanozyme-catalyzed products [70]. To overcome the limitation of incomplete lesion ablation in conventional electrotherapies, Lee et al. developed a pulsed electric field strategy based on Ti₃C₂ MXene. This strategy successfully integrated physical electroporation with nanozyme catalysis. The Ti₃C₂ MXene adhering to the surface of cancer cell membranes functions as a local field enhancer. Upon the application of PEF, the high electrical conductivity (67.5 S cm⁻¹) and 2D lamellar structure of the MXene generated a pronounced concentration of current density and electric field strength at the edges of nanosheet (Figure 3E). This local intensification led to the formation of high-energy electrical hotspots, the transmembrane potential (TMP) was rapidly elevated, resulting in irreversible depolarization and the formation of nanopores. Meanwhile, under electrical stimulation, the peroxidase (POD)-like activity of MXenzyme was markedly enhanced. The robust generation of •OH triggered extensive lipid peroxidation, further compromising the integrity of the cell membrane [71]. However, this input mode requires sophisticated hardware, specifically complex pulse generators, to ensure the

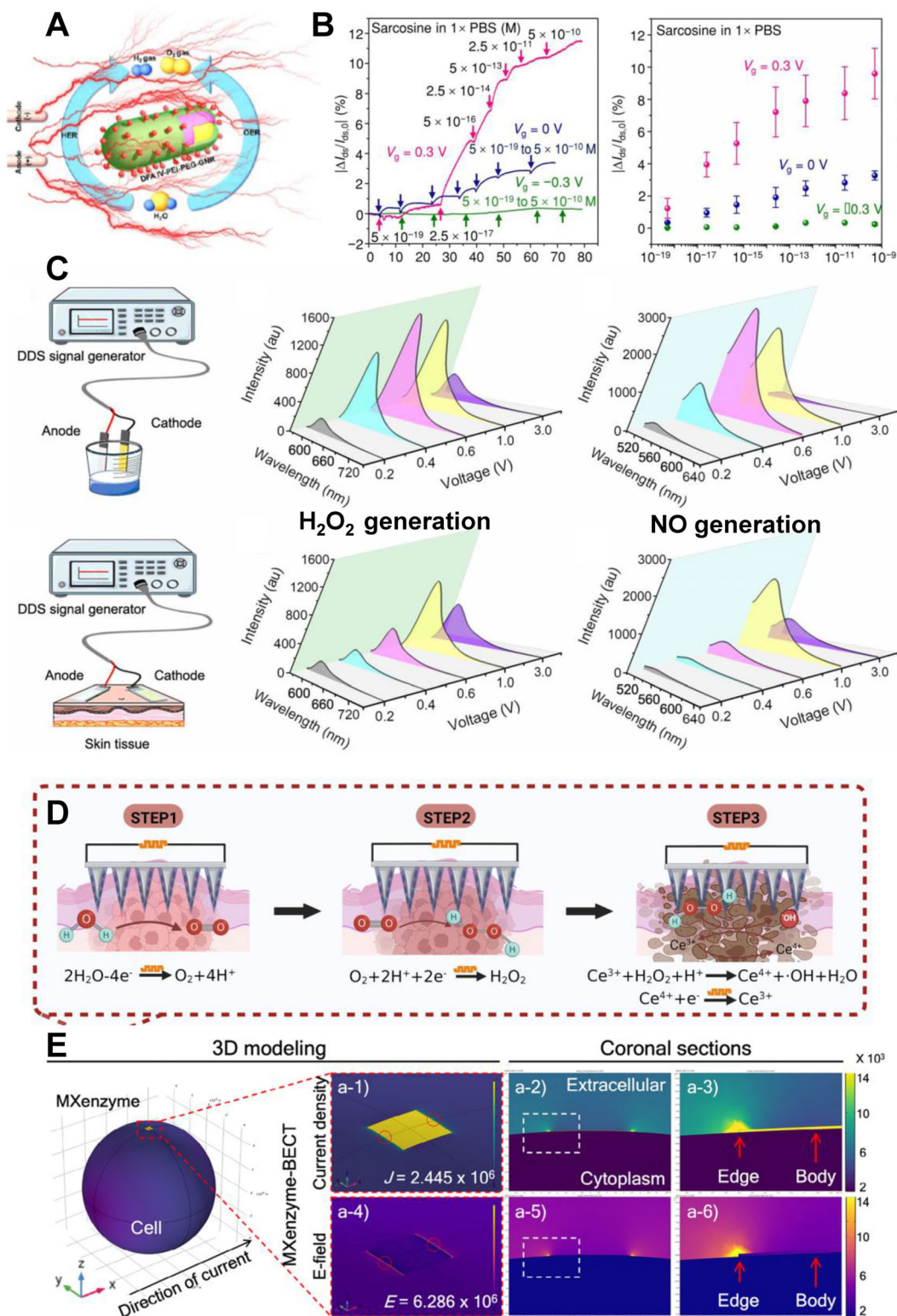


FIGURE 3 | Application of direct external electric fields for nanozyme modulation. (A) Schematic illustration of distinct reactions driven by direction-dependent electric fields. Reproduced under terms of the CC-BY license [62]. Copyright 2024, The Authors, published by American Chemical Society. (B) Influence of direction-dependent potentials on enzymatic activity. Reproduced under terms of the CC BY-NC license [63]. Copyright 2023, The Authors, published by American Association for the Advancement of Science. (C) Schematic of the DC power supply-bio-tissue interface and the effect of the DC electric field on H₂O₂ and NO generation. Reproduced under terms of the CC-BY license [64]. Copyright 2025, The Authors, published by American Association for the Advancement of Science. (D) Schematic illustration of electric field-enhanced catalytic therapy using ZCG. Reproduced with permission [67]. Copyright 2025, Wiley-VCH. (E) Simulation of the interaction between pulsed electric fields and MXene. Reproduced under terms of the CC BY-NC-ND license [71]. Copyright 2025, The Authors, published by Wiley-VCH.

highly precise transmission of high-voltage and high-frequency pulses.

The main advantage of direct external electric fields is the digital controllability of electrical parameters. The electric fields can be precisely modulated by utilizing the key parameters (voltage amplitude, frequency, waveform, and duration) of external circuitry, thereby enabling quantifiable regulation of nanozyme activity. However, the clinical translation of this modality has been hindered by the physical constraints of wired connectivity. Furthermore, the nonspecific electrolysis *in vivo* may generate toxic species like hypochlorite, which poses a critical safety hazard [62].

3.2 | Ultrasound-Mediated Piezoelectric Fields

The *in situ* conversion of mechanical energy into electric fields is a pivotal strategy for achieving wireless and noninvasive modulation, and is particularly suitable for deep-tissue therapy [72]. Utilizing US as an energy carrier to generate *in situ* electric fields is a promising wireless strategy. Owing to its superior tissue penetration, US can reach deep-seated pathological sites noninvasively [73]. This acoustic energy is can be converted into a local microelectric field at the interface of piezoelectric nanozymes [74]. Mechanistically, the piezoelectric effect is triggered by the internal charge separation within non-centrosymmetric crystal materials (e.g., BaTiO₃, ZnO, and MoS₂) under mechanical stress [75, 76]. When US interacts with piezoelectric nanoparticles, the acoustic pressure causes lattice deformation, forcing the relative displacement of positive and negative charge centers to generate a piezoelectric field [77]. Furthermore, the resulting internal electric field (IEF) will trigger the band bending of nanozymes. This band modulation effect drives the migration of electrons and holes towards opposite directions, effectively suppressing recombination of charge carriers and overcoming the energy barrier of unfavorable thermodynamic reactions [78]. The field intensity and catalytic efficacy of these US-mediated piezoelectric fields are depended on the synergy between acoustic input parameters and intrinsic material properties. The electric field and catalytic reaction can be controlled by adjusting the ultrasonic frequency and power density [79].

The primary advantages of US-PEF lie in its noninvasiveness and deep-tissue penetration [80]. These properties substantially extend the application scope of nanozyme-mediated treatments. Furthermore, by avoiding the implantation of electrodes, the infection risks and biocompatibility issues can be effectively avoided. Peng et al. developed a Ru-doped Bi₄O₅Br₂ nanosheet system for US-triggered therapy [81]. Upon the US exposure, due to the enhanced piezoelectric field, the position of the conduction band was optimized, thereby augmenting the reduction ability. The generated electrons were captured by oxygen vacancies (Ov) and rapidly transferred to O₂ adsorbed on Ru sites. This process significantly enhanced the POD-like activity, leading to a robust production of •OH and O₂^{•-}, and facilitating the efficient clearance of deep bacterial abscesses and biofilms (Figure 4A).

3.3 | Pyroelectric Fields

Electric fields can also be established by leveraging temperature variations. In response to temperature fluctuations, instantaneous high-intensity surface charges and electric fields are generated on the surface of pyroelectric materials, which is caused by the alterations in spontaneous polarization [82]. The thermal stimulation can be converted into electrical signals to drive the catalytic activity of nanozymes. During the heating phase ($dT/dt > 0$), the dipole alignment is disrupted by thermal disturbance, the spontaneous polarization and surface adsorbed charge density decrease. To restore the electrostatic equilibrium, the surface shielded charges will be released to generate a transient pyroelectric current or potential. On the contrary, during the cooling phase ($dT/dt < 0$), a reverse flow of compensatory charges is driven by the enhanced polarization, producing an opposite electrical output [83]. By leveraging this property, noninvasive electric fields can be induced by thermal fluctuations, such as body temperature variations or temperature gradients between focal and healthy tissues. In this way, the necessity of invasive electrode implantation is obviated, and the clinical safety will be significantly improved [84].

For example, Meng et al. utilized hBT-CuS@PDA to achieve the *in vivo* pyroelectric effect through the thermal energy derived from near-infrared (NIR) irradiation [85]. The POD-like and glutathione peroxidase-like (GPx) activities of CuS were significantly enhanced by the pyroelectric field. This process effectively facilitated the generation of •OH and depletion of glutathione (GSH). Moreover, the asymmetric distribution of PDA established a temperature gradient across the nanoparticles under NIR irradiation. This asymmetric thermal field induced a thermophoretic force, facilitating the penetration of nanozymes through the physiological barriers of tumor tissue (Figure 4B). Compared with traditional thermal therapy that relies on temperature increase, which poses a significant risk of thermal damage to surrounding healthy tissues [86], alternating cold stimulation offers a safer approach. For example, Zou et al. developed an intelligent system based on Bi₂Fe₄O₉ nanosheets (NSs), which utilizes a remotely controlled electrical device to deliver alternating cold stimulation within the 4–37°C range on the skin surface [87]. The COMSOL finite element simulation demonstrated that under this alternating cold stimulation, a pyroelectric potential of up to 3.1 V was generated on the surface of the nanosheets. Driven by this pyroelectric field, the glutathione oxidase (GSHox)-like activity of Bi₂Fe₄O₉ was significantly potentiated. This catalytic activity follows Michaelis-Menten kinetics, and its rate is directly modulated by the frequency of thermal fluctuations, thus enabling on-demand activation of the catalytic process (Figure 4C).

Despite its promising potential, the pyroelectric regulation in biomedical applications faces serious intrinsic limitations. The primary disadvantage is the transient dependence on temperature variations. Specifically, the generation of electric fields requires continuous and cyclic thermal stimulation, which necessitates complex instrumentation and complicates the control of the treatment. Furthermore, the precise regulation of thermal amplitudes in specific local areas *in vivo* remains a major technical bottleneck [88].

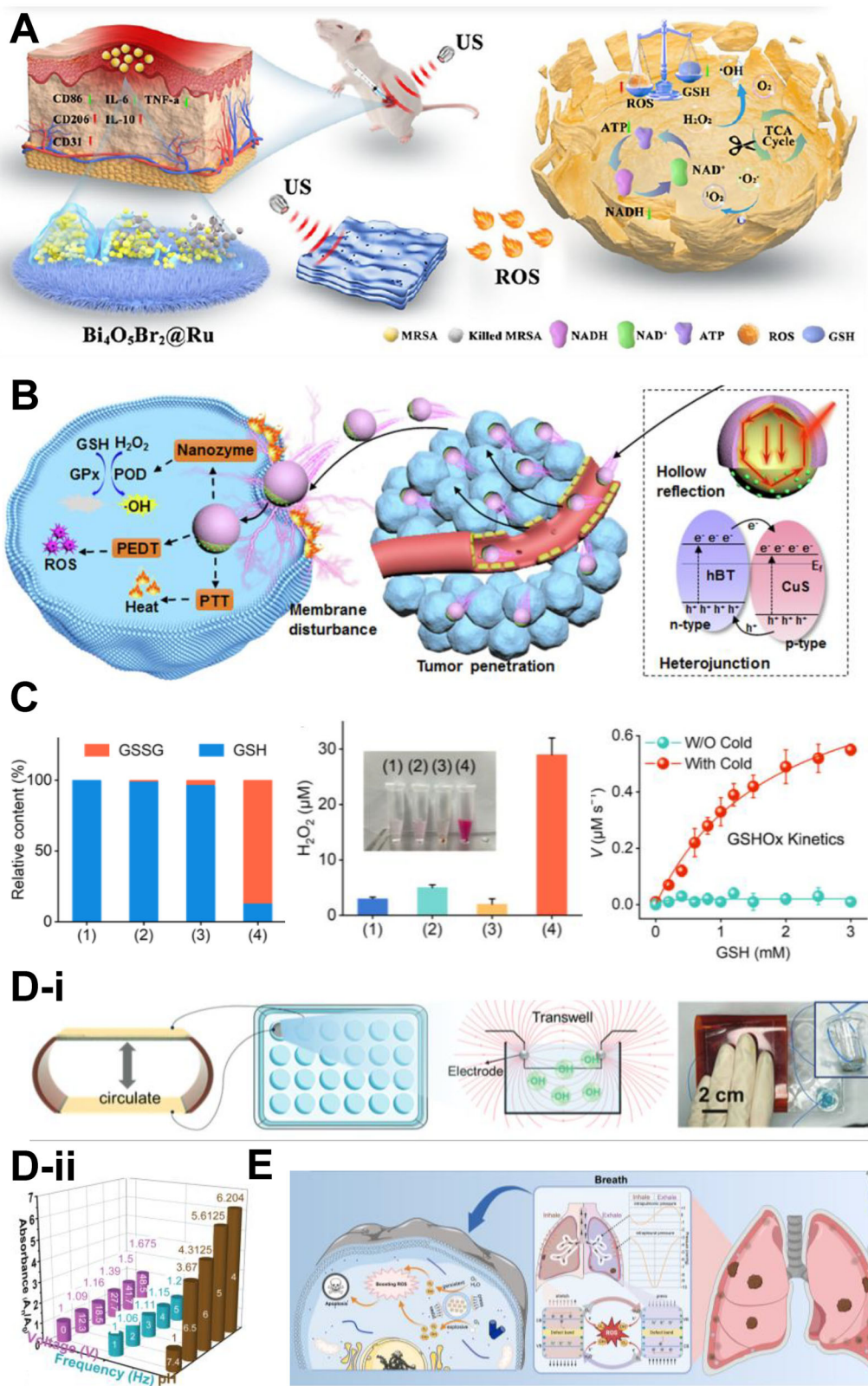


FIGURE 4 | Modes of electric field for nanozyme modulation. (A) Schematic illustration of ultrasound-mediated piezocatalytic therapy for treating deep-seated MRSA-infected abscesses. Reproduced with permission [81]. Copyright 2025, American Chemical Society. (B) Schematic of pyroelectricity-activated nanozymes for tumor therapy. Reproduced with permission [85]. Copyright 2024, Elsevier. (C) Effect of cold treatment on the catalytic activity of $\text{Bi}_2\text{Fe}_4\text{O}_9$ NSs nanozymes. Reproduced with permission [87]. Copyright 2022, American Chemical Society. (D-i) Schematic experimental setup of CS-TENG-enhanced hCOF enzymatic catalysis; (D-ii) the POD-like activity of hCOF under various voltages and frequencies. Reproduced with permission [95]. Copyright 2024, Wiley-VCH. (E) Schematic illustration of intrathoracic pressure-triggered nanozyme therapy. Reproduced under terms of the CC BY-NC-ND license [96]. Copyright 2025, The Authors, published by Springer Nature.

3.4 | Self-Driven Electric Fields

Self-powered electric fields represent a more advanced technology compared to those aforementioned systems that rely on external energy sources. The core of this technology lies in the designed nanodevices, which can convert endogenous biomechanical energy into electric fields. This energy originates from biological sources such as respiration, heartbeat, or muscle contraction [89]. Physical signals generated by pathological states can also be utilized for this conversion [90]. Consequently, a self-sustaining electrical environment for nanozyme-mediated catalysis can be established without external power supplies. These electric fields are primarily generated through the triboelectric effect and the endogenous piezoelectric effect. Among them, the triboelectric mechanism is based on the coupling of contact electrification and electrostatic induction. During the contact process caused by physical movement, electrons will spontaneously transfer between materials with different electron affinities [91]. Upon separation, equal and opposite static charges will accumulate on their respective surfaces. Therefore, a potential difference will be generated between these surfaces, which drives the electron flow through an external circuit [92].

Triboelectric nanogenerators (TENGs) are considered a classic example of self-powering technology [93]. For the regulation of nanozyme, the unique high-voltage and low-current output of TENGs enables the effective reconfiguration of surface electron cloud distributions without compromising the integrity of biological tissues [94]. For instance, a wearable TENG integrated with a fully π -conjugated covalent organic framework nanocages (hCOF) nanozyme was utilized for cancer therapy [95]. When the fingers tap or the arm swings, TENG can generate an open-circuit voltage (V_{OC}) of 10–50 V. The application of these electrical signals to the hCOF triggered a rearrangement of the electron cloud at the active site (Figure 4D-i). The experimental results confirmed that the POD-like activity of hCOF was enhanced 2.44-fold under self-powered pulse stimulation, effectively eliminating breast cancer cells (Figure 4D-ii). Furthermore, by taking advantage of electrostatic forces and hydrogen bonding between the nanocage pores and drug molecules (doxorubicin), the on-demand drug releases the action of self-driven electric field was achieved. Distinct from TENGs that harvest surface mechanical energy, piezoelectric systems are capable of transducing internal pressure fluctuations within pathological tissues into the electric field. In specific pathological scenarios, such as malignant pleural effusion (MPE), the intrapleural pressure exhibits periodic fluctuations ranging from 10 to -3 mmHg during the respiratory cycle. Xu et al. developed a piezoelectric nanozyme, Yb-UIO-66, which utilized this intrapleural pressure to generate an electric field for the treatment of MPE and the inhibition of tumor growth [96]. This electric field, induced by physiological pressure, drove the separation of electrons and holes and triggers a ROS storm. This therapeutic strategy avoids the distress associated with the repeated thoracic punctures in conventional chemotherapy and enables sustained in vivo treatment for up to 5 days (Figure 4E). Furthermore, both the MPE volume and the pleural tumor growth were effectively suppressed, significantly extending the survival of the mice.

Unlike traditional electric fields, the energy supply of self-driven electric fields mainly relies on passive activation and changes in

the external mechanical environment. Although this paradigm eliminates the dependence on external energy, its application boundaries are inevitably limited by its own properties. The electric field intensity fluctuates significantly with physiological changes, causing unpredictable stochasticity in the catalytic output of nanozymes. Furthermore, there is a frequency mismatch between low-frequency (< 1 Hz) biomechanical energy and the continuous excitation required for efficient nanozyme catalysis [97]. This disparity constrains the peak instantaneous catalytic kinetics, rendering the system less effective than externally applied electric fields in high-intensity burst therapies (e.g., acute ablation) [98]. However, these unique characteristics may endow the system with substantial potential for the long-term management of chronic diseases [49].

4 | Mechanisms of Electric Field Regulation of Nanozymes

The application of an electric field functions far beyond a switch. It fundamentally reshapes the physicochemical environment of the catalyst. As a physical force, the electric field changes the microscopic electronic environment, thereby determining the macroscopic catalytic performance.

4.1 | Modulation of the Electronic Structure of Nanozymes

The application of an electric field serves as a profound physical perturbation that fundamentally reshapes the microscopic electronic environment of the catalyst. The electric field remodels the foundational electronic descriptors of the nanozyme, such as d-band center, surface charge distribution, active-site coordination states, and band structure. These structural rearrangements lay the microscopic foundation for the ultimate macroscopic catalytic performance.

4.1.1 | D-Band Center

The d-band center serves as a pivotal indicator for modulating the catalytic process in metal-based nanozyme therapy, as it determines the interaction strength between nanozymes and adsorbent [99]. According to the Hammer-Nørskov model, the energy of the d-band center relative to the Fermi level determines the occupancy of antibonding states during adsorption, thereby modulating the bond strength between the nanozyme and the substrate [100]. Ideally, the catalyst-substrate interaction must balance the reactant activation and product desorption, which can be optimized by an electric field acting as a precise lever [101]. The electric field determines the interfacial electronic coupling by regulating the displacement of the d-band center, thus becoming the fundamental mechanism for regulating the catalytic performance of nanozymes.

In brief, the d-band center can be shifted by an applied electric field, which all alter the hybridization between metal d-orbitals and adsorbate p-orbitals. The adsorption of key intermediates will be adjusted towards the thermodynamic optimum. For example, a self-driven TENG was employed to stimulate a copper single-atom nanozyme (Cu-NC) [102]. After applying a 20 V electric

field, the electron cloud was redistributed, characterized by a significant increase in electron density near the Fermi level, and the d-band center was up-shifted from -3.414 to -3.375 eV. This electronic regulation enhanced the orbital overlap between the d-orbitals of Cu and the p-orbitals of the substrate (H_2O_2), effectively reducing the adsorption energy barrier for H_2O_2 from 0.38 to 0.1 eV. This regulation enhanced the catalytic kinetics and therapeutic efficacy, increasing the tumor suppression rate from 14.8% to 63.4% (Figure 5A). Similarly, in the MoS_2 - MoSe_2 heterostructure, the catalytic process was effectively enhanced through the regulation of the d-band center mediated by the built-in electric field (BIEF) [103]. BIEF guides the electrons to transfer directionally toward the MoS_2 domain, shifting the d-band center of Mo atoms upward from -4.36 to -4.23 eV. Consequently, the adsorption energy of the Li_2S_6 intermediate was optimized from -0.89 to -0.95 eV, further validating the efficacy of d-band center adjustment (Figure 5B).

4.1.2 | Surface Charge

Surface charge serves as pivotal bridge connecting the macroscopic electric field and microscopic reaction kinetics. It not only guides the substrate transport through electrostatic forces, but also actively modulates the energy pathways of elementary reactions by redefining the activation energies [104]. The electric field causes the redistribution of charge carriers (e^- and h^+) at the nanozyme interface for reshaping the thermodynamic environment and kinetic barriers of catalytic reactions [105, 106].

The activation energy (E_a) of elementary catalytic steps can be drastically altered by the accumulation of specific surface charges. In the piezoelectric material MoS_2 , an electric field was generated through surface charge polarization via ultrasonic stimulation. Density functional theory (DFT) calculations revealed that these charges critically regulate the catalytic mechanism [107]. The energy barrier for H_2O decomposition on a neutral MoS_2 surface is 2.27 eV. However, this barrier was decreased to 1.85 eV and 0.93 eV in the presence of positive and negative surface charges, respectively. The reason is that positive charges strengthened the chemical bonding of adsorbed OH species, while negative charges facilitated the transfer of electrons to the hydroxyl group. These effects synergistically promoted H_2O_2 dissociation and $\cdot\text{OH}$ generation (Figure 5C). Moreover, Zhang et al. demonstrated that the catalytic activity of nanozymes can be directly enhanced by free electrons [108]. Under the US-mediated electric field, the GOx-like activity of hBT@Au-G increased from 72.4 to 134.9 U mg^{-1} . And this enhancement was completely suppressed by adding $\text{K}_2\text{Cr}_2\text{O}_7$ as an electron-trapping agent, confirming the pivotal role of electrons in this amplified enzyme activity (Figure 5D).

4.1.3 | Dynamic Activation and Regeneration of Active Sites

In addition to the static modulation of electronic properties (e.g., d-band center and surface charge), the external electric fields also dynamically reconstruct and regenerate the active sites of nanozymes. Specifically, electric fields facilitate the regeneration

of active sites and promote the formation of highly reactive species.

The sustained catalytic activity of nanozymes can be achieved through the regeneration of active sites driven by electric field. For instance, in polyphenol-based antioxidant therapies, the scavenging of RPS typically leads to the irreversible oxidation of active phenolic hydroxyl groups into inactive quinone substances, thereby causing the rapid loss of therapeutic efficacy. Ran et al. demonstrated that the quinone groups of polyphenol nanozymes can be regenerated into their active phenolic form through external electrical stimulation [109]. A regenerative antioxidant system capable of sustained ROS scavenging was established by these electric field-driven nanozymes for overcoming the stoichiometric limitations of traditional antioxidants (Figure 5E).

Furthermore, the electric field can also regulate the metastable high-valence species to enhance the activity of the nanozyme. In multi-metallic alloy nanozymes (e.g., PtMnIr), specific valence states (e.g., Mn^{3+} and Ir^{3+}) act as catalytic hotspots in cascade reactions. But they are often unstable or scant under equilibrium conditions. Li et al. revealed that the application of an AC field disrupted the surface electronic equilibrium, significantly increased the surface proportion of these highly active “spark” species ($\text{Mn}^{3+}/\text{Ir}^{3+}$) (Figure 5F) [110]. This regulation led to a significant increase in enzyme activity and tumor suppression. Furthermore, in heterogeneous piezo-self-Fenton (EPSF) systems, the piezoelectric electrons generated from the built-in electric field were rapidly captured by lattice metal centers (e.g., Fe^{3+}), accelerating the rate-limiting reduction step ($\text{Fe}^{3+} \rightarrow \text{Fe}^{2+}$) [111]. This process eliminated the kinetic bottleneck of the iron cycle and ensured continuous progress of the Fenton reaction. Thus, the electric field acts as both a regulator and energy pump, maintaining the catalyst in a state of high-energy and biological activity.

4.1.4 | Band Structure

The electronic band structure dictates the thermodynamic feasibility of ROS generation, where the relative positions of the conduction band minimum (CBM) and the valence band maximum (VBM) determine the reduction and oxidation capabilities of e^- and h^+ , respectively [112, 113]. To achieve the generation of ROS, the band edges must thermodynamically straddle the requisite redox potentials: the CBM should be more negative than -0.33 V (vs. NHE) for $\cdot\text{O}_2^-$ evolution, while the VBM should be more positive than $+2.10$ V (or $+1.49$ V) for $\cdot\text{OH}$ production from H_2O or H_2O_2 [114]. However, the therapeutic efficiency of nanozymes is frequently constrained by the mismatch of intrinsic band structures. To address this limitation, an electric field can be employed as a regulating handle to adjust the band structure.

With the electric field is applied, a space charge layer will form at the interface, driving the bending of the energy band equilibrate the system. Specifically, the direction of this bending is dictated by the polarity of the accumulated surface charges: negative charges induce upward bending, whereas positive charges result in downward bending [115]. In ReS_2 nanozymes, the band structure was effectively modulated by the US-mediated piezoelectric field

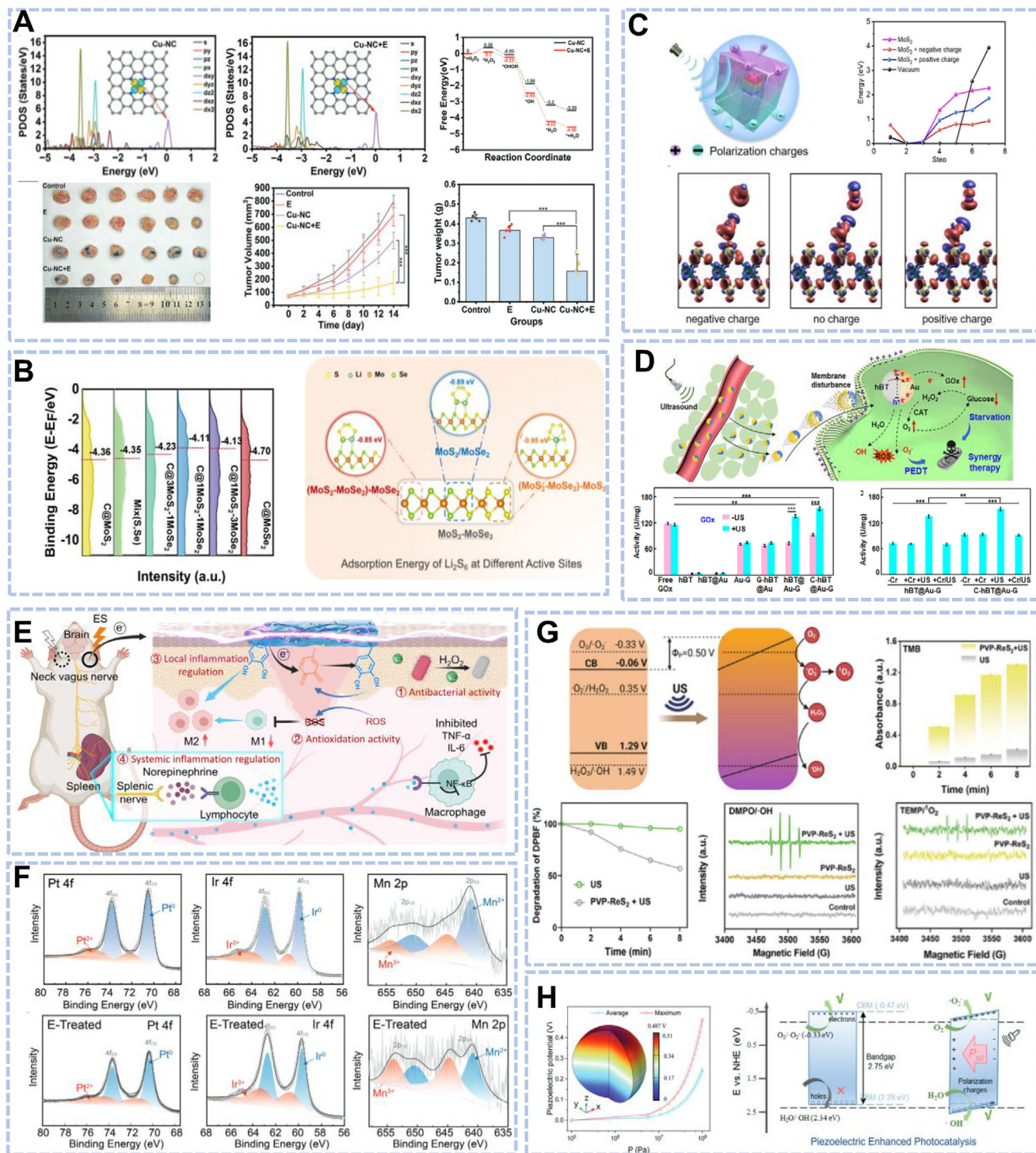


FIGURE 5 | Modulating nanozyme electronic structure by electric fields. (A) TENG-mediated d-band center modulation for boosting Cu-NC nanozyme activity. Reproduced with permission [102]. Copyright 2023, Wiley-VCH. (B) Adsorption of intermediates on MoS₂-MoSe₂ optimized by d-band center tuning. Reproduced under the terms of the CC-BY license [103]. Copyright 2025, The Authors, published by Wiley-VCH. (C) Nanozyme catalysis modulated by electric field via surface charge regulation. Reproduced with permission [107]. Copyright 2022, Wiley-VCH. (D) Nanozyme activity enhanced by free electrons. Reproduced with permission [108]. Copyright 2025, Wiley-VCH. (E) Electric field-driven sustained catalysis of nanozyme-enhanced redox hydrogel. Reproduced with permission [109]. Copyright 2025, Wiley-VCH. (F) XPS spectra of PtMnIr nanozymes before and after electric field treatment. Reproduced with permission [110]. Copyright 2025, Wiley-VCH. (G) Nanozyme activity enhanced by electric field-induced band structure modulation. Reproduced with permission [116]. Copyright 2024, American Chemical Society. (H) Band bending induced by piezoelectric potential. Reproduced with permission [117]. Copyright 2024, Wiley-VCH.

[116]. A significant bending and shifting of the energy bands were induced, the CBM shifted from -0.06 to -0.56 V (vs. NHE), and the VBM shifted from +1.29 to +1.79 V. The requisite redox potentials were reached via the realignment of band edges. This optimization substantially broadened the redox window, thereby significantly amplifying the ROS generation (Figure 5G). For the case of Hf-MOF, the correlation between electric potential and band structure evolution was visually corroborated via COMSOL simulation [117]. It was revealed that a piezoelectric potential was established under ultrasonic activation, which directly led to a substantial reconstruction of the energy bands. Finally, the VBM of Hf-MOF was modulated to a sufficiently positive potential, enabling the generation of $\cdot\text{OH}$ that was previously unattainable, causing the effective disruption of biological membrane structures (Figure 5H).

Overall, the potential and effectiveness of using electric fields to regulate nanozymes are well demonstrated by the effects of electric fields on these electronic descriptors. These microscopic electronic descriptors synergistically drive the macroscopic catalytic performance of the nanozyme.

4.2 | Modulation of the Catalytic Process

The catalytic efficiency of nanozymes fundamentally depends on the thermodynamic and kinetic barriers across the multi-step cycle from substrate adsorption and activation to product desorption. The electric fields serve as a universal and precise physical tuning knob to overcome these limitations. The catalytic process of nanozyme is optimized by the restructuring of the microscopic electronic structure under electric fields. Herein, the fundamental mechanisms of electric field-regulated catalytic processes are dissected, with a focus on the regulation of substrate adsorption and activation and the mitigation of reaction energy barriers.

4.2.1 | Substrate Adsorption

The catalytic cycle typically begins the enrichment process of substrate molecules from the bulk solution to the active sites, which facilitates the formation of transition states [118]. The adsorption of substrate on nanozymes can be directly modulated by electric fields. Through this regulation, the local substrate concentration at the active sites is elevated, thus enhancing the overall catalytic efficiency. Specifically, electric fields induce the polarization of the interfacial electron cloud, which strengthens noncovalent interactions (e.g., van der Waals and electrostatic forces) [119–121], becoming the thermodynamic driving force for substrate accumulation and effectively reducing the energy barrier for adsorption.

In a study utilizing the $\text{Fe}_3\text{O}_4@\text{ZIF-8}@\text{Ag}$ nanocomposite, the adsorption rate of the target molecule acetamiprid (AAP) was substantially accelerated with the application of a -0.5 V DC potential, and the adsorption efficiency increased by 8.6-fold [122]. Density functional theory (DFT) calculations elucidated the underlying microscopic mechanism: the external field strengthened the van der Waals interactions between AAP molecules and the ZIF-8 ligands, and more binding sites were simultaneously

formed (Figure 6A). The computational results indicated that the Gibbs free energy of electro-driven adsorption becomes $-16.52 \text{ kcal mol}^{-1}$, which was more negative than that of static adsorption ($-13.58 \text{ kcal mol}^{-1}$), confirming the enhanced thermodynamic driving force. Furthermore, the electric field causes the direct injection of electrons from the nanozyme surface into the antibonding orbitals of adsorbed substrates, leading to the weakening or cleavage of the intrinsic chemical bonds. This electronic regulation process was monitored by Chen et al. via Bader charge analysis [123]. It was indicated that 1.49 electrons were implanted into the antibonding orbitals of H_2O_2 under the influence of the electric field. The O–O bond was significantly weakened and elongated, resulting in a reduction in bond energy and a substantial promotion of H_2O_2 adsorption (Figure 6B).

4.2.2 | Reaction Energy Barrier

After substrate enrichment and activation, the catalytic process is required to overcome the reaction energy barrier to generate the product. This barrier represents the rate-limiting step of the reaction kinetics. It can be regulated by the electric field, which can stabilize transition states characterized by charge separation or significant dipole moments through electrostatic interactions, thereby resulting in a substantial reduction of the reaction energy barrier [105, 124].

Take the Hemin-BTO nanozyme as an example, the electronic structure of the active center was precisely modulated by the spontaneous polarization electric field of ferroelectric BaTiO_3 (BTO) [125]. DFT calculations revealed that this built-in electric field induced a downshift of the overall d-band center to lower energy levels. Consequently, the Gibbs free energy (ΔG) for the formation of the key intermediate $\cdot\text{O}$ transitioned from an endothermic state (0.102 eV) of pure BTO to a strongly exothermic state (-2.612 eV) of Hemin-BTO (Figure 6C). By reshaping the thermodynamic landscape, the activation energy of the rate-determining step was drastically reduced. A catalytic constant (K_{cat}) of $1.41 \times 10^6 \text{ s}^{-1}$ was achieved for H_2O_2 , which was 400-fold higher than that of natural horseradish peroxidase (HRP). This electric-field driven mechanism overcomes the intrinsic kinetic inertness of nanozymes, thereby enabling superior reaction kinetics.

Compared to the intrinsic electric field of ferroelectric materials, an external electric field offers a more direct strategy for regulating the energy barrier in the catalytic process. In the self-powered Ru nanozyme (Ru1000) system, the d-band center of Ru was effectively regulated by an electric field [126]. It shifted closer to the Fermi level, thereby promoting the transfer of active electrons. The verification through DFT calculations shows that the energy landscape of the reaction pathway was significantly altered by the applied electric field. The adsorption energy of H_2O_2 was lowered from -0.5 to -0.9 eV, which significantly strengthened the adsorption and rendered the process more thermodynamically spontaneous. Crucially, the energy barrier of the rate-determining step was reduced by stabilizing key intermediates. Specifically, the adsorption energy of $\cdot\text{OH}$ was adjusted from -1.38 to -1.63 eV under the application of an electric field. This stabilization of the intermediate effectively lowered the activation energy barrier for

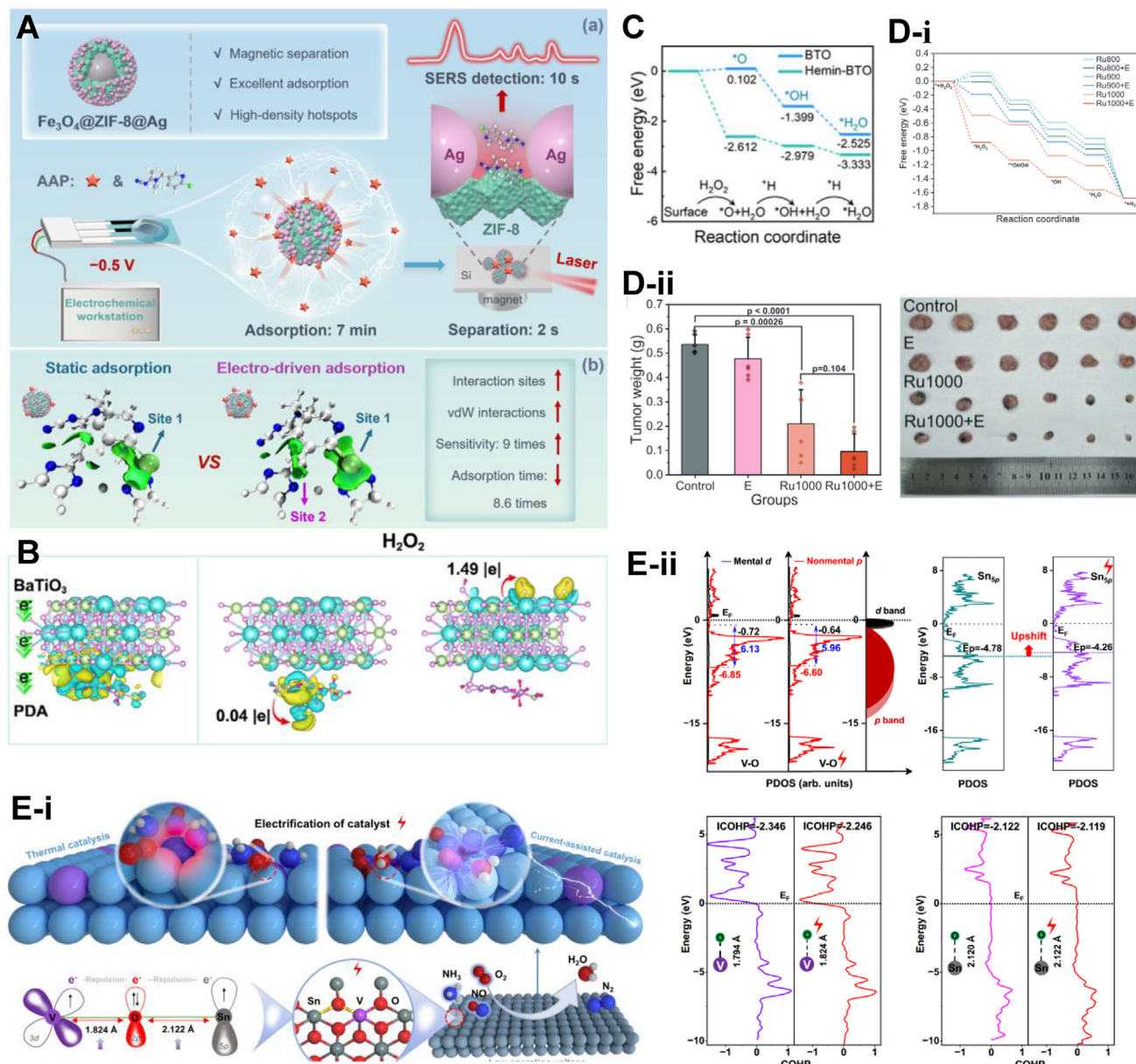


FIGURE 6 | Modulating the catalytic process of nanzyme by electric fields. (A) Schematic of APP adsorption on $\text{Fe}_3\text{O}_4@\text{ZIF-8}@\text{Ag}$ promoted by electric field. Reproduced with permission [122]. Copyright 2025, Elsevier. (B) Bader charge calculations for the adsorption of H_2O_2 on BaTiO_3 . Reproduced with permission [123]. Copyright 2025, Wiley-VCH. (C) Energy profile for POD-like activity of BTO and Hemin-BTO. Reproduced with permission [125]. Copyright 2025, American Chemical Society. (D-i) Effect of electric field on the reaction energy barrier of RUX POD-like catalysis; (D-ii) effect of electric field on tumor growth over a 14-day period. Reproduced under the terms of the CC BY-NC-ND license [126]. Copyright 2024, The Authors, published by Springer Nature. (E-i) Schematic of weak electric current-assisted catalysis over 2VNA catalysts; (E-ii) influence of weak current-induced electron migration on bond weakening in 2VNA: DOS and COHP analyses. Reproduced under the terms of the CC BY-NC-ND license [127]. Copyright 2024, The Authors, published by Springer Nature.

the decomposition of H_2O_2 into $\cdot\text{OH}$ (Figure 6D-i). Notably, this strategy enhanced the antitumor efficacy, increasing the tumor inhibition from 61% to 82% (Figure 6D-ii).

Distinct from the regulation of d-band centers, the current-driven electronic shear effect offered an alternative strategy for adjusting the energy barriers in nanzyme catalysis. In a weak current-assisted single-atom V catalyst (2VNA) system, electrons were directionally driven by a weak external current ($< 1\text{ A}$) and selectively enriched near the single-atom V active sites. This

localized electron injection increased the electron occupancy of V-O antibonding orbitals (Figure 6E-i). The integrated crystal orbital Hamiltonian population (ICOHP) increased from -2.346 to -2.246 (a decrease in absolute value), indicating a weakened bonding interaction. (Figure 6E-ii). The strength of the V-O chemical bond was effectively reduced by this electronic shear effect. The reaction energy barrier for the rate-determining step, the release of lattice oxygen, was significantly reduced. Thus, an efficient catalytic cycle was realized under this ultra-low temperature conditions driven by this current [127].

5 | Material Strategies for Enhancing the Electric Field-Nanozyme Interaction

Although electric fields can regulate nanozyme catalysis by modulating electrical parameters, the effectiveness of this regulation is not entirely determined by the electric field itself. It is also constrained by the coupling efficiency between the electric field and the nanozyme. Within this binary system, the electric field serves as an external driver for energy input and direction guidance, while the nanozyme material functions as the energy transducer and reaction executor. Due to intrinsic physical properties of the materials, such as low dielectric constant, weak polarization capacity, and high charge-transport resistance, the energy generated from the electric field may be dissipated as heat before reaching the active sites. Therefore, rational material design is essential for bridging the macroscopic external field and microscopic catalytic reactions, which can minimize energy-transfer losses and improve the field-nanozyme coupling efficiency. This section will delve into material strategies, including defect engineering, rectifying interface engineering, and conductive interface engineering, to optimize the response of the material to electric fields, as well as the rectification and transport of charge.

5.1 | Defect Engineering for Intrinsic Field-Responsiveness

Many nanozymes exhibit limited intrinsic responsiveness to external electrical stimuli due to constraints such as weak polarization capability or unfavorable electronic structures. Defect engineering can modulate dielectric properties and electronic band structure by disrupting lattice symmetry, inducing local dipoles, tuning electronic structures, and creating unsaturated coordination sites [128, 129]. Chemical reduction, high-temperature annealing, plasma etching, or heteroatom doping methods can purposefully introduce specific types of defects with certain concentrations and spatial distributions into the nanozyme lattice [130]. These modifications allow for the pre-programming of electronic structures, which effectively amplifies the coupling between the material and electrical signals.

Crystal defects, especially vacancies, are regarded as pivotal functional components in electrocatalysis. Under the influence of electric field regulation, they play a triple role: narrowing the bandgap to facilitate excitation, acting as charge traps to inhibit carrier recombination, and providing unsaturated coordination sites for substrate activation [131, 132]. Chen et al. achieved a dramatic enhancement in piezocatalytic performance by incorporating Ov into the SBN lattice and coupling it with SNO to form a heterojunction [133]. The bandgap was significantly narrowed after introducing Ov, and the excitation of electrons from the valence band to the conduction band was facilitated by the electric field. Crucially, Ov functions as deep-level traps that effectively locks electrons in a separated state to extend their lifetime (Figure 7A-i). Furthermore, this material design enhanced the activation of substrates. The local high electron density at Ov site promoted the transfer of e^- to adsorbed O_2 , leading to the efficient generation of $\cdot O_2^-$. The experimental result confirmed that the production of singlet oxygen (1O_2) in SBN/SNO-Ov system was 7.4-fold higher than that of pristine SBN (Figure 7A-ii).

Similarly, black $BaTiO_3$ (B-BTO) was synthesized by introducing Ov through hydrogenation reduction method, resulted in the formation of Ti^{3+} species and a reduced bandgap (from 2.81 to 1.9 eV) (Figure 7B-ii) [134]. Under the US-induced electric field, Ov facilitated the transport of charge to the surface and lowered the potential threshold required for driving redox reactions.

The electrical properties of the material have also been enhanced by the introduction of vacancies. Mondal et al. demonstrated that the introduction of sulfur vacancies (Sv) can increase the piezoelectric coefficient (d_{33}) from 23.5 to 29.7 pm V $^{-1}$ and the piezoelectric potential (V_p) from 0.22 to 0.38 V (Figure 7C-i) [135]. In MoS_2 , the lattice typically exhibits centrosymmetry. This local symmetry was disrupted by the removal of S atoms, resulting in the permanent displacement of positive and negative charge centers, thereby generating more local dipole moments. This enhancement in electrical performance is attributed to the superposition of local dipoles induced by vacancies under mechanical strain and macroscopic polarization (Figure 7C-ii). Yang et al. synthesized three types of $ZnIn_2S_4$ nanosheets with distinct Sv concentrations (ZIS-2, ZIS-4, and ZIS-8) by regulating the concentration of thioacetamide [136]. As the sulfur vacancy concentration elevated, the piezoelectric coefficients of these materials progressively increased from 21.6 to 46.7 mV V $^{-1}$ (Figure 7D-i). Furthermore, the higher Sv concentrations effectively suppressed the recombination of electron-hole pairs (Figure 7D-ii). The efficiency of charge separation and transport were also enhanced through this defect engineering of the material (Figure 7D-iii). These findings provided further robust evidence for the significant influence of Sv engineering on the electrical properties of materials.

Defect engineering improves the coupling effect between the electric field and nanozymes by enhancing the intrinsic field-responsiveness of the catalyst. The defects not only increase the ability of materials to generate or respond to local electric fields, but also prolong carrier lifetime and create reactive sites for substrate activation. Therefore, defect engineering provides a route to connect the electrical polarization, charge separation, and catalytic cycle within the nanozyme system.

5.2 | Rectifying Interface Engineering for Directional Charge Separation

Single-component nanozymes usually require a balance between physical properties and chemical activity. For instance, perovskite materials with high piezoelectric coefficients (e.g., $BaTiO_3$) are typically wide-bandgap insulators with high charge transport impedance [137]. While highly active catalysts lack enough responsiveness to mechanical or thermal stimuli. To overcome these limitations, rectifying interface engineering (e.g., heterojunction) has been utilized to combine multiple materials with distinct electronic band structures or conductivities [138]. By establishing an internal electric field or low-impedance path at the interface to enhance charge transfer and precisely rectify the charge flow, it will ensure that the energy is efficiently converted into chemical driving force.

When two semiconductors with differing Fermi levels contact with each other, it will lead to electron transfer and Fermi level

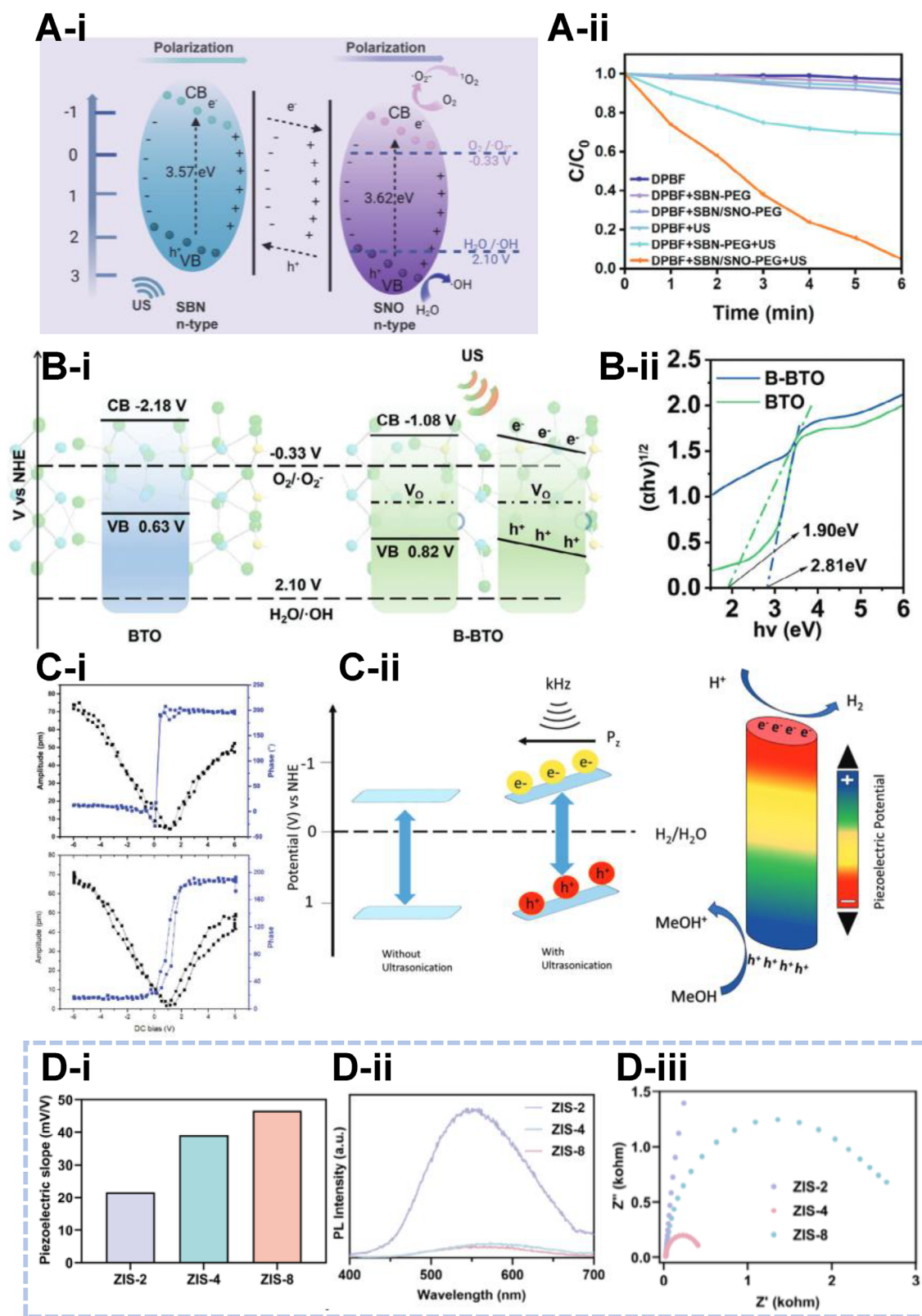


FIGURE 7 | Material strategy of defect engineering for enhanced nanozyme-field coupling. (A-i) Schematic energy band diagram of Ov-enhanced ROS generation in SBN/SNO under US irradiation; (A-ii) degradation kinetics of DPBF by $^1\text{O}_2$ under ultrasound-induced piezoelectric field. Reproduced with permission [133]. Copyright 2024, Wiley-VCH. (B-i) Schematic illustration of Ov-enhanced ROS generation in piezo-activated BTO; (B-ii) effect of Ov introduction on the band gap energy of BTO. Reproduced with permission [134]. Copyright 2025, Wiley-VCH. (C-i) Phase characterization and hysteresis loops of MoS_2 before and after Sv introduction; (C-ii) schematic illustration of the mechanism for Sv-enhanced H_2 production under electric field. Reproduced with permission [135]. Copyright 2025, Wiley-VCH. (D-i) Piezoelectric coefficients, (D-ii) e^-h^+ recombination efficiency, and (D-iii) EIS spectra of samples with different Sv concentrations. Reproduced with permission [136]. Copyright 2025, Wiley-VCH.

alignment. This process causes the energy bands at the interface and creates a space charge region, resulting in an intrinsic electric field. When the direction of this electric field is aligned with the polarization electric field induced by external mechanical or thermal stimuli, a stronger driving force is formed through superposition effect. Wei et al. constructed a heterojunction using zinc porphyrin (ZnTCPP) and hollow barium titanate (hBT) [139]. The difference in Fermi levels induced an intrinsic interfacial electric field (IEF) directed from ZnTCPP to hBT. An alternating electric field was excited by US, with its direction periodically aligning with the IEF to produce a synergistic enhancement effect. When the US-induced electric field was aligned with the IEF (ZnTCPP→hBT), the superimposed strong electric field drove the reaction between electrons on hBT and holes on ZnTCPP. This driving force directed the most potent redox carriers to participate in the catalytic process. On the contrary, when the electric field direction was reversed, the reaction pathway transformed into a Type-II heterojunction, which facilitated the generation of $\cdot\text{OH}$ and O_2^- (Figure 8A).

The Schottky barrier formed at the interface between semiconductor and metal functions as a one-way valve. During the half-cycle, electrons are pumped from the semiconductor into the metal, and the barrier will physically hinder the electrons from flowing back, leading to the accumulation of active electrons at the reaction sites of the nanozymes. Based on this principle, Cheng et al. constructed an Au-ZnO Schottky junction to achieve efficient atherosclerosis therapy [140]. When electrons flowed from ZnO to Au, the Schottky barrier impeded the backflow of electrons into the conduction band of ZnO and prevented their recombination with holes in the valence band. This resulted in a prolonged lifetime and accumulation of electrons on the surface of Au nanoparticles (Figure 8B). The catalytic activity of these Au sites rich in electrons was significantly enhanced, improving the generation efficiency of ROS.

Rectifying interface engineering can improve the coupling effect between the electric field and the nanozyme, which will determine where charges migrate and how effectively charge recombination is suppressed. Through the effects of built-in electric fields, band bending, and Schottky barriers, rectifying interfaces can transform randomly generated or rapidly recombined carriers into directionally separated reactive charges.

5.3 | Conductive Interface Engineering for Low-Loss Charge Transport

Unlike rectifying interface engineering, conductive interface engineering focuses on reducing transmission losses and transporting charges to catalytic sites. The intrinsic impedance of the materials is a critical but frequently neglected factor in the design of electric field-regulated nanozymes. With the application of an electric field, high resistance will lead to severe Ohmic losses and carrier recombination. This challenge can be effectively addressed by anchoring, encapsulating, or growing nanozymes on a conductive framework with high electron mobility (e.g., graphene, graphdiyne, MXene, carbon nanotubes, or conductive polymers) [34, 141, 142]. As an electron attractor, the conductive substrate rapidly extracts and transports excited electrons to the surface, significantly suppressing the bulk recombination.

Graphdiyne (GDY), a novel 2D material comprising sp - and sp^2 -hybridized carbon atoms, possesses both excellent conductivity and a rich porous structure. ZnO@GDY nanorods were constructed by Bai et al. to effectively enhance the coupling efficiency between electric fields and nanozymes [143]. Under US stimulation, piezo-electrons were generated within the ZnO core. The GDY shell facilitated the instantaneous transfer of electrons from the ZnO conduction band to the surface through its high carrier mobility. In addition, the recombination of electron-hole pairs was physically inhibited, leading to an extension of carrier lifetimes by several orders of magnitude. Furthermore, the interfacial charge transport resistance was significantly reduced by the built-in electric field established at the ZnO-GDY interface (Figure 8C). Through the incorporation of GDY, the activation efficiency of H_2O_2 increased by 20.7-fold compared to pure ZnO, enabling the rapid disinfection of wounds infected with multidrug-resistant bacteria. Besides, Guo et al. developed a ZnO@HTCS system, attaching ZnO onto hydrothermal carbon spheres (HTCS) as a conductive carrier, which was used to treat deep infections requiring enhanced electric field-responsiveness [144]. By the introduction of HTCS, the interfacial electron transfer was significantly accelerated, as evidenced by DFT calculations. A 99.7% killing efficiency against methicillin-resistant *Staphylococcus aureus* (MRSA) was achieved within 15 min of US treatment, effectively managing the osteomyelitis therapy (Figure 8D).

Conductive interface engineering provides a design principle for preserving charges by minimizing transport resistance. By constructing low-resistance interfaces between field-responsive components and catalytic sites, this strategy enables rapid charge extraction and transfer before charge recombination, thereby improving the utilization of electrical stimuli in nanozyme catalysis.

Overall, these strategies focus on optimizing the entire process of electric field response, charge rectification, and transport during the electric field-nanozyme coupling. Defect engineering enhances the intrinsic field responsiveness of nanozymes by amplifying their response to electrical stimuli or promoting local electric-field generation. Rectifying interface engineering improves the utilization of field-generated charges by directing their migration and spatial separation. Conductive interface engineering further lowers transport impedance and reduces charge dissipation during their transfer to the catalytic site. These strategies provide a useful framework for understanding and improving the coupling efficiency between electrical stimuli and nanozyme catalysis.

6 | Electric Field-Driven Nanozymes for Precision Therapy

The activity of nanozymes can be significantly enhanced by electric fields through the dynamic optimization of electronic structures and catalytic processes. However, therapeutic efficacy is not determined by catalytic activity alone. There is still critical mechanistic gap between field-enhanced catalysis at the nanozyme surface and biological outcomes in complex physiological environments. The electric field-regulated nanozyme may interact with cell membranes, ion channels, mitochondria,

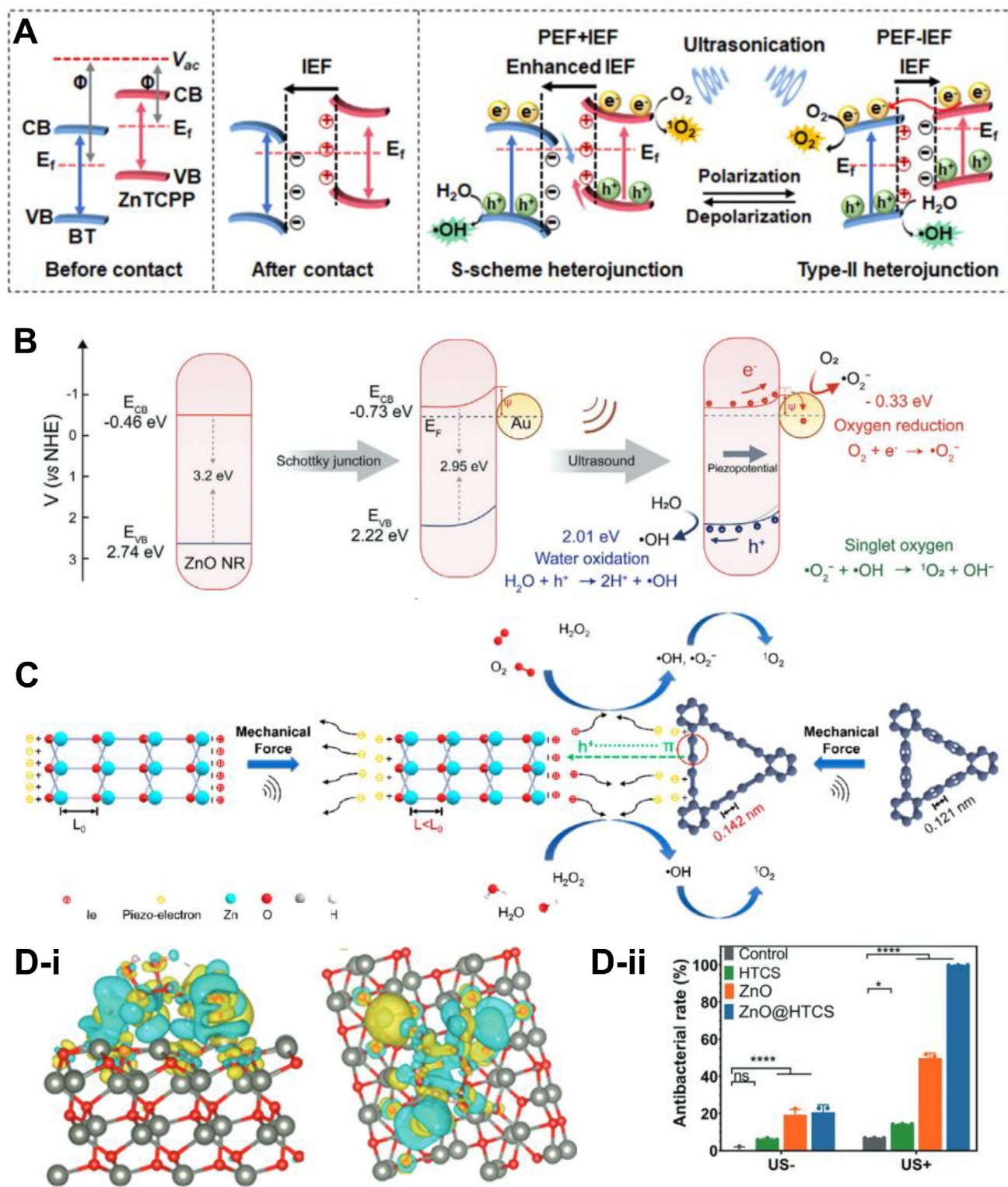


FIGURE 8 | Material strategy of interface engineering for enhanced nanozyme–field coupling. (A) Schematic illustration of carrier migration induced by the built-in electric field (IEF): The distinct electric field distributions result in direction-dependent IEFs between hBT and ZnTCPP, enhancing both the IEF intensity and charge transfer mechanisms. Reproduced with permission [139]. Copyright 2025, Wiley-VCH. (B) Schematic diagram of the bandgap analysis of Au-ZnO Schottky junction and its piezocatalytic mechanism under US activation. Reproduced with permission [140]. Copyright 2024, Wiley-VCH. (C) Schematic Illustration of the Carrier Migration at the ZnO@GDY NR Interface [143]. Copyright 2022, American Chemical Society. (D-i) The simulation of the differential charge diagram for Zn (101) load HTCS: (left) side view, (right) top view; (D-ii) effect of HTCS introduction on antibacterial rate. Reproduced with permission [144]. Copyright 2024, Wiley-VCH.

immune cells, extracellular matrix, and bacterial biofilms in vivo. A clarification of the biological mechanisms underlying electric field-nanozyme interactions is necessary. This section discusses the biological mechanisms of electric field-modulated nanozymes and explores their potential as catalytic modulators in precision therapy.

6.1 | Biological Mechanisms of Electric Field-Regulated Nanozyme Therapy

Therapeutic efficacy is not determined by catalytic activity alone, the field-enhanced catalytic must be translated into biological responses in cells, tissues, and pathological microenvironments. Due to the limited direct cellular and molecular evidence, the biological mechanisms of electric field-regulated nanozyme therapy may be discussed by drawing on related principles from electrochemical catalysis, nano-bio interface, and electrophysiology. From this perspective, the electric field-regulated nanozyme therapy represents a coupled bio-nano process involving electrical input, interfacial catalytic activation, local redox remodeling, and downstream cellular signaling [145].

The dynamic interaction at the nanozyme-bio interface plays a crucial role in the treatment process [146]. At the nanozyme-biofluid interface, the electric-activated nanozyme can be regarded as a localized electrochemical microreactor rather than a passive catalytic particle. The surface of nanozymes in physiological fluids is surrounded by ions, water molecules, proteins, and substrates, possibly forming an interfacial region similar to the electrical double layer in electrochemistry [147]. Guided by the theory from electrochemical catalysis, the biological mechanisms underlying electric field-nanozyme interactions may be interpreted and inferred. In this confined region, electric fields may redistribute ions, orient water dipoles, alter local proton activity, and regulate electron transfer. These effects are particularly important for oxidoreductase-like nanozymes, as their catalytic cycles usually involve electron transfer, proton-coupled reactions, and the activation of O_2 , H_2O_2 , H_2O , or GSH [148–150]. Specifically, with a local potential gradient across this boundary, the electric field will selectively enrich or exclude charged substrates, antioxidants, and intermediates, thereby changing their effective concentrations at the catalytic site [151–153]. Meanwhile, the electric field can reorganize interfacial water near the surface of nanozyme, effectively reshaping the hydrogen-bond network and thereby regulating proton transfer and the activation of H_2O/H_2O_2 at the catalytic site [154, 155].

The plasma membrane is one of the earliest biological structures capable of sensing the electrical and redox perturbations generated at the nanozyme-cell interface [156]. The electrical and chemical signals can be transduced into intracellular signals through changes in membrane potential, ion channels, and Ca^{2+} influx [157, 158]. In electric field-regulated nanozyme therapy, this interface may be disturbed through two coupled processes. On the one hand, the electric field can directly alter membrane polarization, local ion distribution, and the opening state of voltage-sensitive channels [159]. On the other hand, electric-activated nanozymes may generate ROS and deplete GSH, leading to the oxidation of membrane lipids and ion channel proteins

[160]. When these electrical and catalytic oxidative perturbations converge in the vicinity of the membrane, lipid oxidation may compromise membrane barrier function and lower the threshold for electric field-induced permeability, thereby exacerbating ionic leakage, Ca^{2+} influx, and downstream mitochondrial stress [161, 162]. The amplified ionic leakage and Ca^{2+} influx can further propagate membrane-localized perturbations to mitochondria, resulting in mitochondrial membrane-potential disruption. Once the redox homeostasis of the mitochondria is disrupted, the initial nanozyme-membrane interfacial signal may be amplified into mitochondrial depolarization, ATP depletion, and regulated cell death [163].

6.2 | Spatiotemporally Regulation

Precise spatiotemporal treatment is crucial for maximizing efficacy and safety. Conventional nanodrugs primarily rely on size-dependent passive targeting and ligand-mediated active targeting [164, 165]. However, its application is restricted by complex physiological barriers and systemic toxicity. Electric regulation endows nanozyme catalytic therapy with unprecedented spatiotemporal precision. Nanozymes can remain in an inert state without an electrical signal and can be activated on demand when an electrical signal is present, thereby enabling the maximum improvement of efficacy and safety.

This precise spatiotemporal control has been demonstrated in previous studies. Chen et al. developed a logic gate nanoplatform modulated by dual inputs of electric field activation and the tumor microenvironment (TME), leading to a notable improvement in therapeutic safety [166]. Specifically, MnO_2 act as an electrical shielding module, which can be unlocked by high levels of intracellular glutathione (GSH). After degradation of MnO_2 , the exposed Pt nanozymes efficiently catalyzed the generation of $\bullet OH$ under an electric field. Strictly following the “AND” logic, the activation of the treatment was confined to the scenario where GSH-mediated MnO_2 unshielding and external electrical stimulation occur simultaneously (Figure 9A-i). The role of electric-field control was supported by a relatively complete set of control experiments. At the cellular level, AC or HMPD alone caused limited cytotoxicity, whereas HMPD+AC markedly increased ROS, mitochondrial dysfunction, caspase-1 activation, GSDMD cleavage, and the release of pyroptotic cytokine. In vivo, AC or HMPD alone showed weak tumor inhibition, whereas HMPD+AC produced the strongest antitumor response (Figure 9A-ii). These controls indicate that electric stimulation acts as a catalytic trigger rather than a nonspecific therapeutic input. By integrating exogenous physical signals with endogenous biochemical factors, this strategy achieved intelligent and precise spatiotemporal control. Dai et al. further extended this concept by developing MIL-100(Fe)@Pt@R837@HA (HMPR) for OSCC therapy [167]. In this system, square-wave AC acted as an on-demand catalytic trigger for Pt-mediated electrodynamic ROS generation, while HA/CD44-mediated tumor accumulation and local electrode placement provided spatial selectivity. The electric field contributed not only to ROS amplification but also to spatiotemporal control of catalytic activation. Compared with the limited effects of only HMPR and only ES controls, HMPR+ES markedly enhanced the treatment.

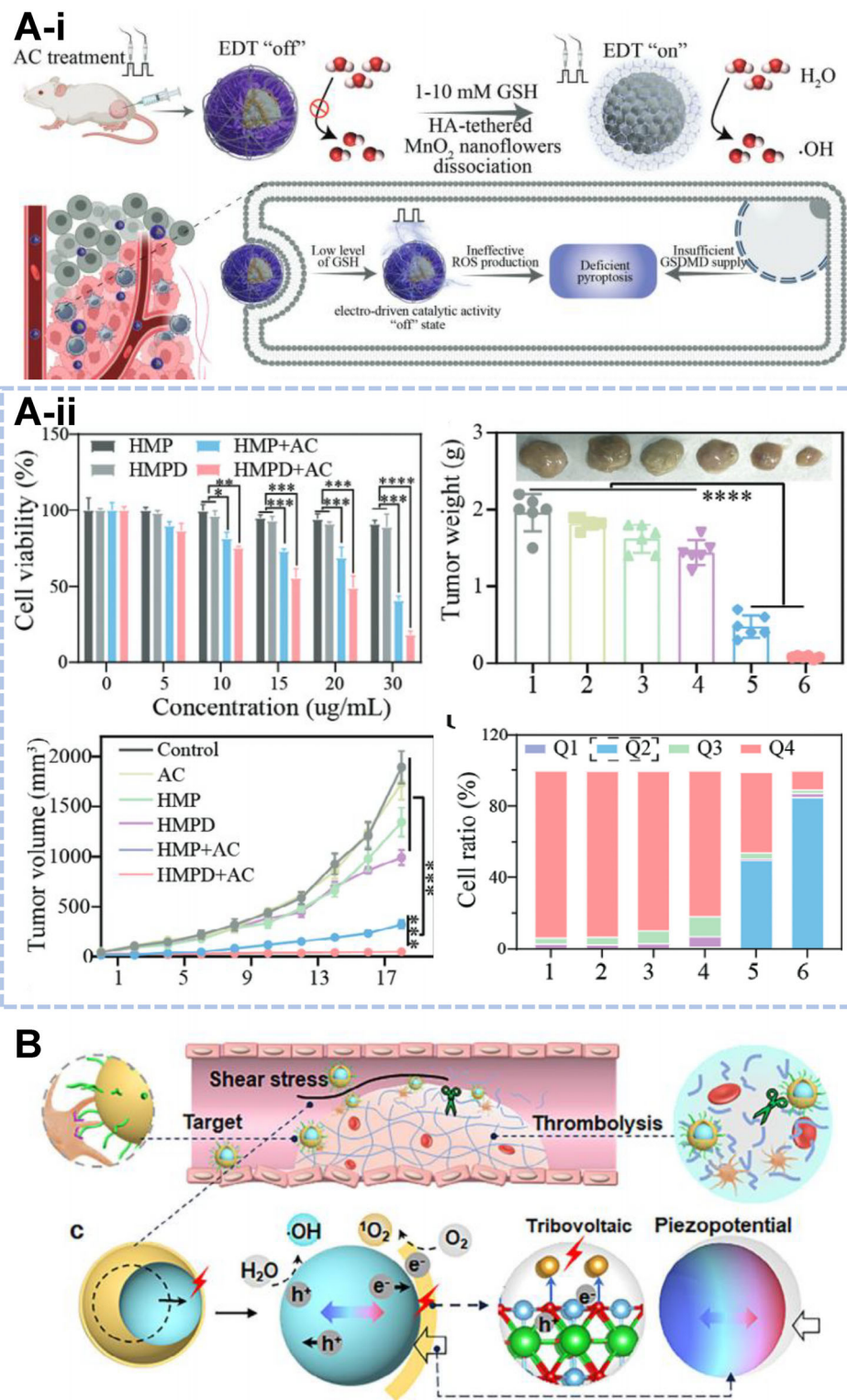


FIGURE 9 | Spatiotemporal therapy via electric field-regulated nanozymes. (A-i) Schematic of the HMPD for spatiotemporal precision therapy; (A-ii) in vivo and in vitro therapeutic effects under different systems. Reproduced with permission [166]. Copyright 2025, Wiley-VCH. (B) Schematic diagram of the synthesis and spatiotemporal precision therapy of tBT@Au-RGD NPs: RGD-mediated targeting and shear stress-induced electric field thrombolysis. Reproduced with permission [168]. Copyright 2025, Wiley-VCH.

The pathological microenvironment can also function as an endogenous trigger to initiate electric fields for regulating nanozymes. Zheng et al. engineered a shear stress-triggered thrombolytic system using yolk-shell tBT@Au-RGD nanoparticles, in which a disease-generated mechanical abnormality was

used as both a lesion marker and an endogenous electrical activation source [168]. Briefly, a tetragonal barium titanate (tBT) core was encapsulated within an Au shell to construct a yolk-shell architecture, which was surface-grafted with RGD peptides to target activated platelets. Under pathological conditions, the

shear stress increased from approximately 10^3 s^{-1} in normal blood vessels to 10^5 s^{-1} . Driven by this high-intensity shear force, the tBT yolk underwent high-frequency collisions and friction against the Au shell. Through the synergistic triboelectric and piezoelectric effects, they collect endogenous mechanical energy to generate electron-hole pairs (Figure 9B). This design was supported by several critical controls. Under non-stenotic shear, the degradation of RhB was negligible, whereas high shear rates markedly increased RhB degradation, $\bullet\text{OH}/^1\text{O}_2$ generation, and thrombolysis. tBT@Au-RGD reduced carotid stenosis to 3.99% with a lower bleeding risk than uPA. This pathological shear stress-governed negative feedback loop enabled precise and self-powered thrombolysis by integrating thrombus-biased accumulation with shear-stress-gated electrocatalytic activation.

6.3 | Quantitative Regulation

In clinical pharmacology, the dosage often dictates whether the drug can cure a disease or become a poison. Precision therapy requires that the therapeutic interventions not only be precisely activated across spatiotemporal scales but also be dynamically regulated in dosage [169]. However, traditional nanozymes become uncontrollable after entering pathological tissues and starting to function. Their enzyme-like activities merely respond passively to the microenvironmental signals and lack active modalities. This passivity often leads to uncontrolled catalytic reactions, posing a risk of indiscriminate damage to normal tissues due to the excessive generation of ROS. However, this limitation can be addressed through electric field-regulated nanozymes. The parameters of electric fields (e.g., voltage amplitude, frequency, and duty cycle) offer a tunable interface to digitize the activity of nanozymes, enabling programmable therapy [170, 171]. By shifting from passive dependence to active control, this strategy transforms stochastic chemical reactions into programmable, dose-precise therapeutics, achieving personalized interventions to maximize efficacy while minimizing systemic risks.

This programmable and quantitative regulation of therapeutic inputs offers a promising strategy for addressing the stage-specific demands of infected wound healing. Wang et al. reported an ultrasound-responsive piezoelectric microfiber system, which provides a clear example of stage-adapted and parameter-programmable catalytic therapy [172]. The Li-doped ZnO/PLLA microfibers converted ultrasound into both sonodynamic ROS generation and local piezoelectric stimulation. The electrical output was quantitatively modulated by variations in ultrasound intensity, and the output voltage increased almost linearly with ultrasound intensity and nanorod content. This parameter-output relationship was further translated into a segmented therapeutic regimen. (Figure 10A-i) In the infection stage, strong ultrasound stimulation (1.5 W cm^{-2} , 15 min) activated sonodynamic antibacterial activity, increasing the killing efficiency against *S. aureus* from approximately 38.4% to 94.2% (Figure 10A-ii) In the subsequent repair stage, mild ultrasound stimulation (0.3 W cm^{-2} , 1 min) provided electrical cues for cell recruitment, Ca^{2+} influx, neurogenesis, and angiogenesis while avoiding excessive oxidative stress. In vivo, the ZnLiPOI+US group achieved approximately 99.0% wound closure by day 12 and 89.9% antibacterial

efficiency on day 6, comparable to commercial Atrauman Ag dressing.

The output electrical parameters of TENGs can also serve as a tunable interface between mechanical input and nanozyme catalysis. In the wearable single-electrode TENG reported by Yao et al., the open-circuit voltage was adjusted from 17 to 50 V by changing the contact pressure from 0.017 to 0.200 N cm^{-2} , while the stimulation frequency could be regulated by the tapping speed (Figure 10B-i) [173]. This mechanically programmable electrical output was then used to regulate the cascade catalytic activity of AuPd alloy nanozymes. The control experiments provide a relatively clear link between electric stimulation and catalytic enhancement. In the CAT-like reaction, electric stimulation increased O_2 generation from H_2O_2 by 1.73-fold. The O_2 output was further increased with the applied voltage increased from 0 to 50 V and frequency from 1 to 5 Hz, supporting a parameter-dependent catalytic regulation (Figure 10B-ii). This catalytic enhancement was further translated into biological outcomes. Electric stimulation alone showed negligible cytotoxicity, as H_2O_2 +E maintained 99.4% 4T1 cell viability, whereas AuPd+ H_2O_2 +E reduced cell viability to 19.4%, lower than AuPd + H_2O_2 without electric stimulation. In vivo, the AuPd+E group achieved 89.5% tumor inhibition, compared with 63.2% for AuPd alone and 18.4% for E alone. (Figure 10B-iii) The TENG-powered electric field-regulated nanozyme shows promise in achieving programmable and quantitative modulation. Moreover, Zhao et al. achieved quantitative control over gas therapy and redox homeostasis using a piezoelectric $\text{MoS}_2/\text{Bi}_2\text{S}_3$ heterojunction [174]. The increase in US power induced a remarkable rise in open-circuit potential, which facilitated efficient H_2 generation and ROS elimination. This process can be quantified by the US power and treatment duration (Figure 10C). In US-mediated piezoelectric nanozymes, Wang et al. also utilized ultrasound as a programmable exogenous input to achieve controlled release of therapeutic agents [175]. The release of CPT exhibited a positive correlation with both US exposure duration and CRB concentration (Figure 10D).

The electric field-regulated nanozymes provide a practical route toward programmable and quantitative catalytic therapy. However, the current level of programmability remains preliminary. In most studies, the reported parameter-output relationships are still established mainly in simplified catalytic assays or short-term cellular models, rather than in heterogeneous and dynamically changing pathological tissues. A more comprehensive framework needs to be established in future research.

6.4 | Microenvironment Reshaping

Nanozyme catalytic therapy is severely hindered by the complex pathological microenvironment [176], characterized by multiple adverse features such as hypoxia [177], high antioxidant levels, dense extracellular matrix (ECM) [178], and high tumor interstitial fluid pressure (TIFP) [179]. Electro-regulated nanozymes can not only adjust the generation of active species but also actively remodel the unfavorable microenvironment, leading to a significant enhancement in overall therapeutic efficacy.

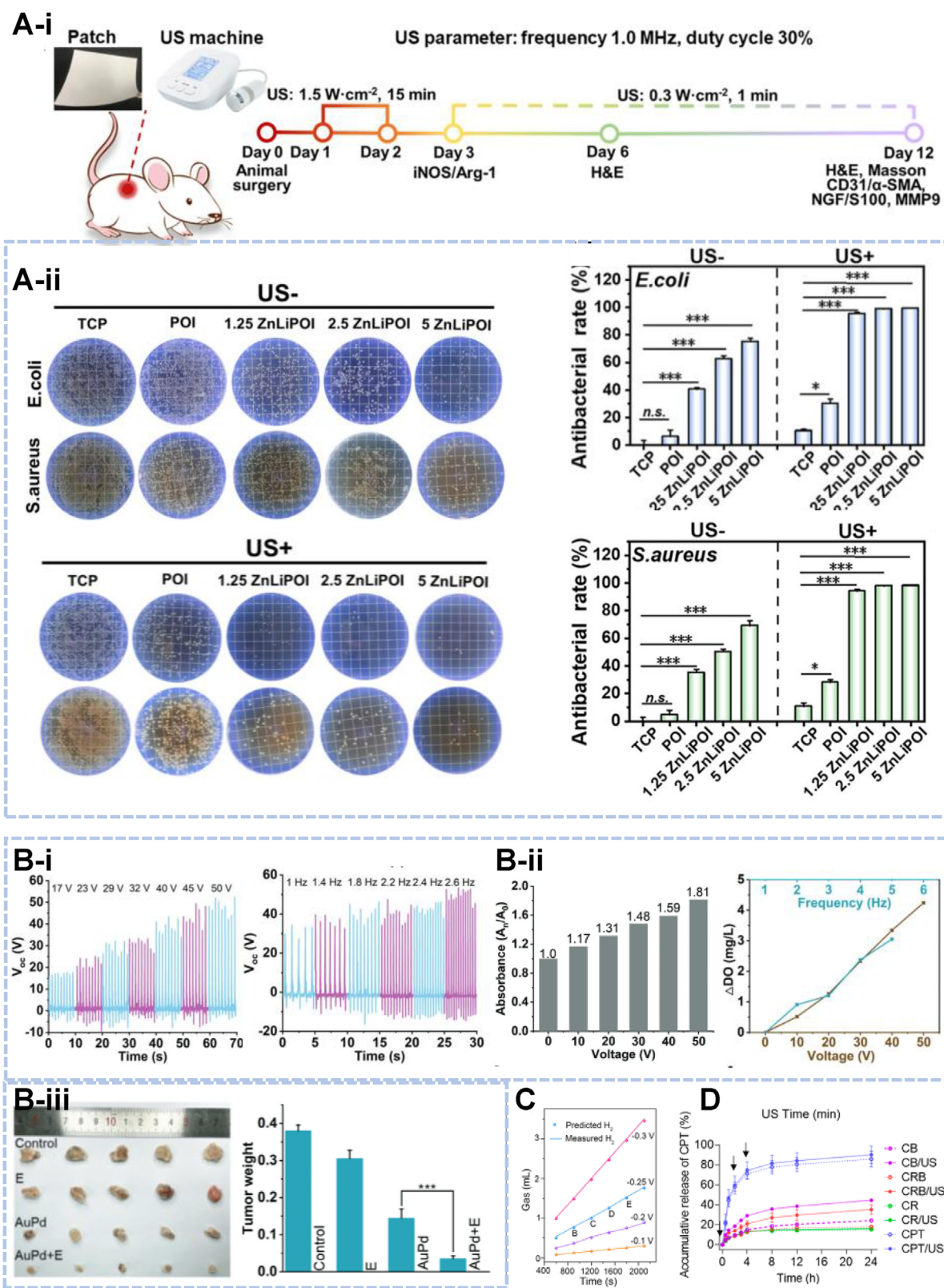


FIGURE 10 | Quantitative therapy via electric field-regulated nanozymes. (A-i) Diagram of intelligent staged therapy for infected wounds enabled by the modulation of US parameters; (A-ii) in vitro antibacterial performance of different groups. Reproduced with permission [172]. Copyright 2024, Elsevier. (B-i) Output voltage of wsTENG under different frequencies and pressures; (B-ii) the CAT-like and GOx-like activities of AuPd nanozymes under different applied voltages; (B-iii) in vivo cancer therapy of AuPd nanozymes under electric stimulation. Reproduced with permission [173]. Copyright 2023, Wiley-VCH. (C) Effects of MoS₂@Bi₂S₃ heterojunction, ultrasound parameters, and concentration on H₂ generation. Reproduced with permission [174]. Copyright 2025, Wiley-VCH. (D) CPT release of CRB nanozymes under different US parameters. Reproduced with permission [175]. Copyright 2023, American Chemical Society.

6.4.1 | Reshaping of Hypoxic Microenvironment

The hypoxic state of the TME poses a significant obstacle to nanozyme-based therapies, as O_2 concentrations are lower than the required level [180]. This directly limits the generation of cytotoxic ROS. Moreover, the sustained hypoxia prompts the enhancement of the antioxidant defenses within tumor cells, which further neutralizes the restricted ROS output and diminishes therapeutic efficacy.

The electric field can directly catalyze water decomposition on the surface of Pt nanozymes to generate $\bullet OH$, bypassing the dependence on O_2 . This is typically achieved through electrodynamic therapy (EDT). Wang et al. developed an LPPI platform for electrically activated oxygen-independent electro-immunotherapy [181]. The central feature of this system is that the electric field directly activates the Pt-Pd core to generate ROS from H_2O rather than O_2 , enabling EDT to remain effective in hypoxic tumor conditions. Under both normoxia and hypoxia, P, LPP, and LPPI produced robust ROS signals with electrical stimulation, while negligible signals were observed in the non-stimulated groups. These results demonstrate that ROS generation relies solely on electrical stimulation, independent of O_2 concentration (Figure 11A). This field-dependent catalytic mechanism was supported by MB degradation assays, in which ROS production increased with current intensity, frequency, and stimulation time. The enhancement of electric field-enhanced catalytic therapy has also been confirmed by control experiments. The LPPI demonstrated superior and sustained tumor inhibition upon electric field application. Wan et al. also achieved effective treatment under hypoxic conditions using oxygen-independent EDT as the core approach (Figure 11B) [182].

Catalase is commonly used to alleviate hypoxia by catalyzing the disproportionation of H_2O_2 into H_2O and O_2 , and this process can be further enhanced by electric fields. Yue et al. developed a POM-based clusterphene nanozyme for remodeling the tumor microenvironment [183]. This system integrates clusters with glucose oxidase (GOx) into a 2D layered structure, thereby coupling tumor microenvironment remodeling with electric field-enhanced nanozyme catalysis. GOx consumes glucose to generate gluconic acid and H_2O_2 , which simultaneously induces nutrient deprivation, acidifies the local microenvironment, and supplies substrates for POD-like catalysis. Meanwhile, the POM-based clusterphene depletes intracellular GSH and exhibits CAT-like activity, contributing to redox imbalance and partial O_2 generation in the tumor microenvironment (Figure 11C-i). The external electric stimulation further enhanced the catalytic output of the clusterphene, as reflected by increased ROS/ $\bullet OH$ generation, improved POD-like catalytic kinetics, enhanced intracellular ROS accumulation, and stronger tumor cell killing (Figure 11C-ii). Mechanistically, this effect is attributed to the electric-field-promoted redox cycling of multivalent W centers within the delocalized 2D clusterphene framework.

6.4.2 | Overcome of Physical Barriers

The therapeutic efficacy of nanomedicines is severely compromised by the physical barriers within the TME, such as the dense

extracellular matrix (ECM) and the elevated tumor interstitial fluid pressure (TIFP), which restrict the deep penetration of therapeutic agents. To overcome these obstacles, strategies of electric field-regulated nanozymes have been developed for active TME remodeling.

In tumor tissues, the ECM undergoes pathological densification and stiffening, a state termed desmoplasia. The essence is that highly cross-linked collagen fibers form a dense physical barrier, which is known as “connective tissue hyperplasia”, resulting in severe limitations on the diffusion of therapeutic drugs [184]. Yu et al. utilized a piezoelectric driven strategy to achieve the degradation of the dense ECM [185]. The Cu_3BiS_3 nanozyme was employed to generate electrical signals under US irradiation, activating the voltage-gated calcium channels (VGCCs) on tumor cell membranes, causing a substantial influx of calcium ions (Ca^{2+}). The calcium-dependent signaling pathway upregulated matrix metalloproteinases (MMP-2 and MMP-9), driving enzymatic degradation of collagen fibers. Compared with other groups, the CBS+US+NIR group exhibited the lowest COL1A1 expression, indicating significant collagen degradation. The removal of the ECM barrier paved the way for the subsequent therapeutic intervention (Figure 12A).

High TIFP is identified as another hallmark of solid tumors. By counteracting the transvascular pressure gradient, this high TIFP can neutralize the driving force for drug delivery, impede the transport of fluid drugs and force therapeutic agents to rely exclusively on slow diffusion for tumor penetration [186]. Electro-regulated nanozymes can alleviate high TIFP by catalyzing water decomposition. This electro-driven process not only alleviates hypoxia but also reduces TIFP through the consumption of interstitial fluid. For instance, a crystalline Fe-doped carbon nitride (CCN-Fe) nanozyme was engineered to catalyze water into H_2 and O_2 under piezoelectric and chemiluminescence excitation [187]. This phase transformation from liquid to gas effectively reduced interstitial fluid volume, significantly lowering the TIFP (approximately 60% of the initial level) (Figure 12B). This reduction in pressure restored the transvascular pressure gradient and facilitated the deep infiltration of immune cells and therapeutic agents. Similar hydrodynamic regulation was also observed in other electro-regulated nanozyme systems. For MoS_2 , this effect significantly improves intratumoral drug accumulation (Figure 12C) [188]. Furthermore, a “nano-lymphatic” system based on pyroelectric catalysis was also developed to alleviate TIFP. The NIR-II laser irradiation induced temperature variations, triggering the pyroelectric effect to initiate water decomposition (Figure 12D-i). The intratumoral water content was reduced from approximately 86.2% to 73.3%. Simultaneously, 52% of the initial TIFP was relieved within 100 min, effectively decreasing the pressure from 38.2 to 18.3 mmHg (Figure 12D-ii). This TIFP downregulation effectively enhanced blood perfusion and drug delivery, achieving a tumor inhibition rate of 93.75% and successfully preventing tumor recurrence [189].

From the above, it can be seen that the therapeutic potential of electric field-regulated nanozymes cannot be assessed only by the extent of catalytic enhancement. It should be critically evaluated based on factors such as target specificity, selectivity conferred by electric-field control, validation depth, parameter-defined controllability, and translational readiness. Meanwhile, the oper-

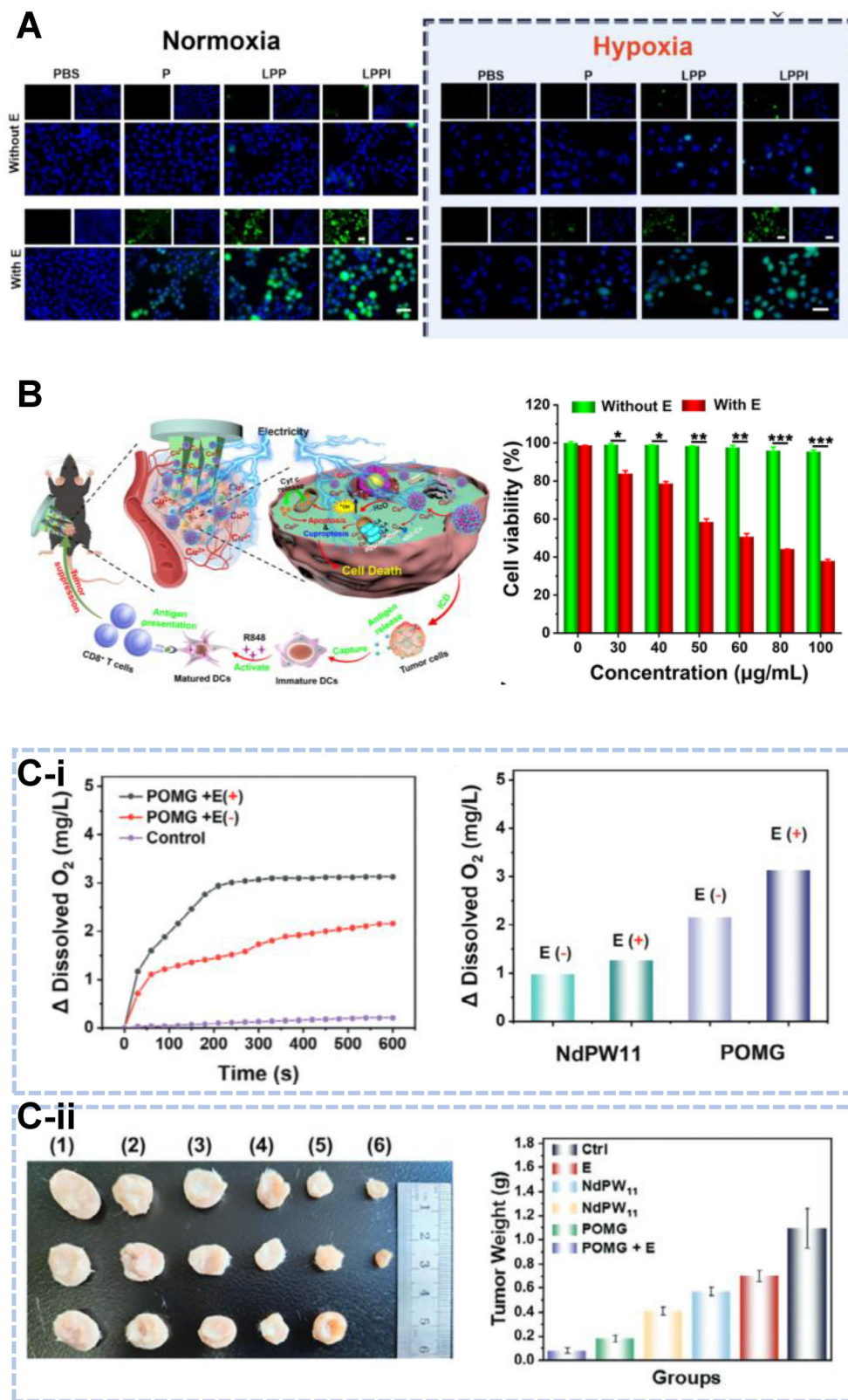


FIGURE 11 | Remodeling hypoxic microenvironment via electric field-regulated nanozymes. (A) The ROS production in a normoxic and hypoxic environment. Reproduced with permission [181]. Copyright 2024, Elsevier. (B) Schematic illustration of electric field-driven direct water oxidation for ROS generation and therapy (left) and cell viability of N-PG with/without EDT under. Reproduced under the terms of the CC BY-NC-ND license [182]. Copyright 2025, The Authors, published by Elsevier. (C-i) The effect of electric field on the CAT-like activity of POMG; (C-ii) antitumor efficacy evaluation of POMG in vivo. Reproduced with permission [183]. Copyright 2024, Wiley-VCH.

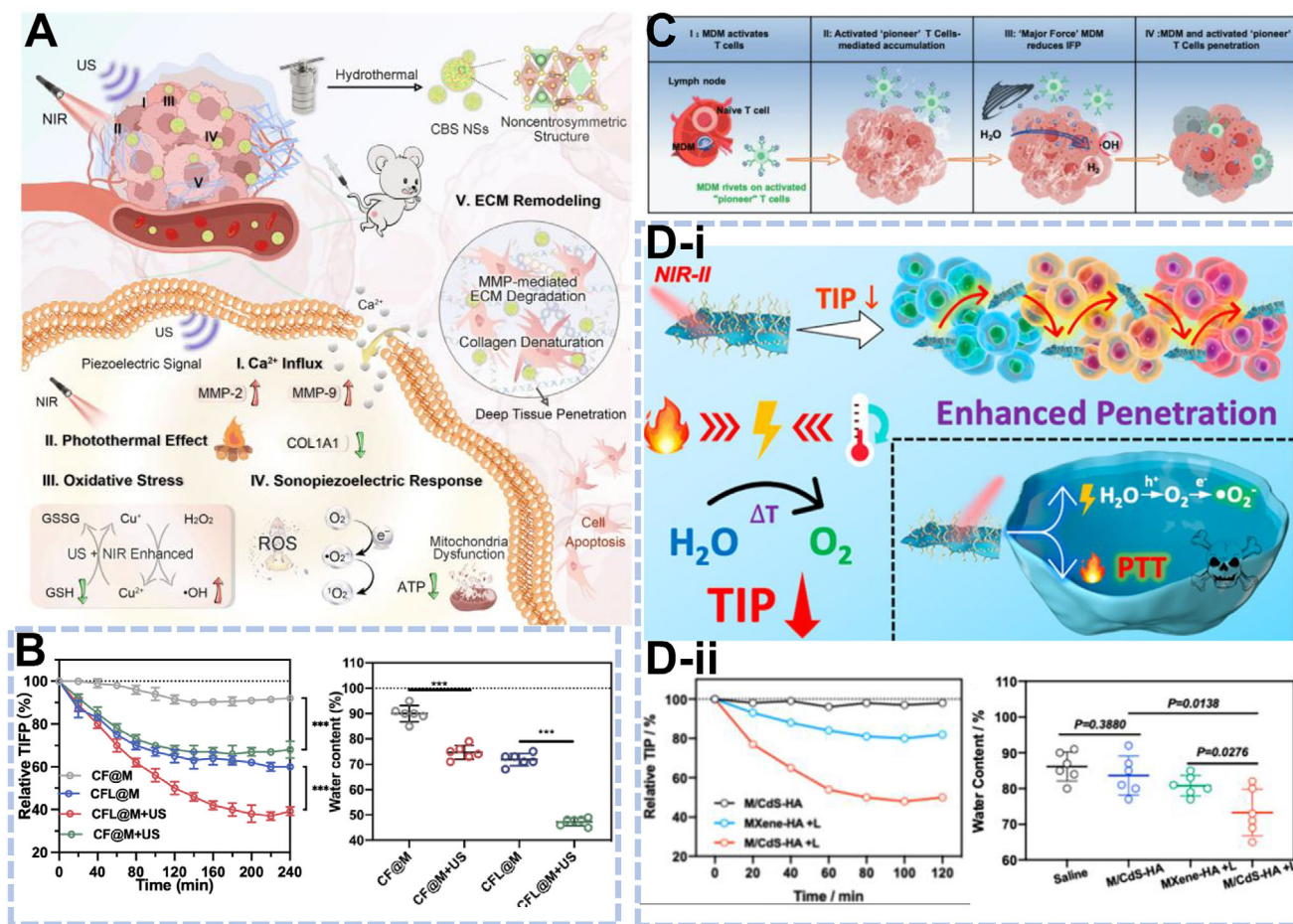


FIGURE 12 | Overcoming physical barriers via electric field-regulated nanzyme for therapy. (A) Schematic illustration of US-driven piezoelectric remodeling of the extracellular matrix for tumor therapy. Reproduced with permission [185]. Copyright 2025, Wiley-VCH. (B) Remodeling of TIFP by CCN-Fe Nanozymes under piezoelectric and photo-excitation CCN-Fe. Reproduced with permission [187]. Copyright 2025, Elsevier. (C) Schematic illustration of TIFP reduction via US-mediated electric fields to enhance the penetration of T cells and nanodrugs. Reproduced with permission [188]. Copyright 2025, Elsevier. (D-i) Schematic of pyroelectricity-driven TIFP reduction for tumor therapy; (D-ii) efficacy of pyroelectric field-activated M/CdS-HA in TIFP Reduction. Reproduced with permission [189]. Copyright 2021, American Chemical Society.

ational parameters of electrical stimulation should be regarded as therapeutic dose variables rather than simple experimental settings. To integrate these considerations at the application and parameter levels, Table 3 summarizes representative systems in the form of an application-parameter matrix.

7 | Summary and Prospects

Despite remarkable progress in fundamental research on the regulation of nanozymes by electric fields, there is still a significant chasm in translating these innovations into clinically feasible and precise medical technologies. To bridge this gap, we critically assess the existing bottlenecks preventing controllability and provide perspectives on feasible future directions for evolving nanozymes into smart, highly precise nanomedicines.

7.1 | Biological Safety

The clinical translation of electric field-regulated nanozymes is hindered by the complex trade-off between catalytic performance

and in vivo biocompatibility, especially for the nanzyme materials containing diverse heavy metal ions [190]. In addition to this chemical toxicity, the impact of this highly active electro-responsive system on biosafety is multifaceted. Many components that are essential for efficient electric field responsiveness (e.g., inorganic piezoelectric substrates or carbon-based conductive networks) are difficult to degrade endogenously [191]. These structurally stable materials will be captured by the reticuloendothelial system (RES), posing severe risks of long-term chronic bioaccumulation and unpredictable off-target catalytic bursts [192]. Furthermore, specific morphological features and the rigid architectures of certain conductive frameworks can induce physical mechanical damage to cellular membranes or trigger inflammation [193–195]. In vivo safety is also influenced by the dynamic evolution at the bio-nano interface. Once in the physiological environment, the high-energy surfaces of these nanozymes spontaneously adsorb plasma proteins, forming a dense protein corona [196]. Under the regulation of electric field, this corona not only acts as a physical and dielectric barrier, hindering the diffusion of substrate and weakening the penetration effect of the local field [197], but also profoundly undermines biosafety. They can trigger unnecessary

TABLE 3 | Integrated application–parameter matrix for electric field-regulated nanozyme therapy.

Nanozyme	Application domain	Field source	Target specificity	Operational parameters	Advantage	Validation status	Translational readiness	Ref.
HMPD	Tumor therapy	AC	GSH, HA/CD44	10 V, 10 mHz, 10 min	Spatiotemporal regulation	87.3% apoptosis, significant tumor inhibition	Early-stage	[166]
HMPR	Tumor therapy	AC	HA, GSH	5 V, 10 mHz, 5 min	Spatiotemporal regulation	Near-complete tumor inhibition	Early-stage	[167]
tBT@Au-RGD	Thrombolysis	Shear stress	RGD	$1 \times 10^5 \text{ s}^{-1}$	Self-powered, on-demand activation, spatiotemporal regulation	91% thrombolysis	Early-stage	[168]
ZnLiPOI	Wound healing	US	Dressing	1.5 W cm^{-2} , 15 min, 0.3 W cm^{-2} , 1 min	Dose-programmable, spatiotemporal regulation	99.0% wound closure	Moderate	[172]
AuPd ANs	Tumor therapy	TENG	Local field	30 V, 1 Hz	Dose-programmable	89.5% tumor inhibition	Early-stage	[173]
MoS ₂ @Bi ₂ S ₃ , @HA	Anti-inflammatory	US	Local injection	$1.5/0.5 \text{ W cm}^{-2}$, 1 MHz, 5 min	Dose-programmable, spatiotemporal regulation	80% TNF- α restraint	Early-stage	[174]
CRB	Tumor therapy	US	EPR	1.5 W cm^{-2} , 1 MHz, 50% duty	Dose-programmable, spatiotemporal regulation	Significant tumor inhibition	Moderate	[175]
LPPI	Tumor therapy	AC	EPR	5 mA, 10 Hz	Oxygen-independent, spatiotemporal regulation	Near-complete tumor inhibition	Early-stage	[181]
N-PG/NSC	Tumor therapy	AC	Local injection	8 mA, 0.1 Hz	Oxygen-independent, spatiotemporal regulation	Significant tumor inhibition	Early-stage	[182]
POMG	Tumor therapy	AC	Local field	5 mA, 5 min	Oxygen-independent, spatiotemporal regulation	80.9% cell death, 92.7% tumor inhibition	Early-stage	[183]
CBS NSs	Tumor therapy	US	EPR	1.2 W cm^{-2} , 1 MHz	ECM remodeling	72.2% apoptosis	Early-stage	[185]
CCN-Fe	Tumor therapy	US	EPR	—	TIFP reduction	60.79% TIFP decreased, 72.6% tumor inhibition	Early-stage	[187]
M/CdSHA	Tumor therapy	NIR-II	HA, CD44	1064 nm, 1.0 W cm^{-2}	TIFP reduction	52.0% TIFP decreased, 93.8% tumor inhibition	Early-stage	[189]

activation of the immune system [198], which is rapidly cleared by macrophages [199], and accumulate in large quantities in healthy organs [200], thereby exacerbating systemic immunotoxicity and unpredictably altering the toxicological profile of the nanozymes [201].

To overcome these multifaceted safety bottlenecks, future research must actively manage the bio-nano interface and the in vivo fate of nanozymes. First, advanced surface engineering, such as the utilization of zwitterionic polymers or biomimetic cell membrane camouflage, can establish a stable hydration layer or provide specific immune-evasive markers [202]. This active disguise effectively suppresses protein fouling and macrophage clearance, without introducing the steric hindrance that typically impairs catalytic responses. Second, to resolve the chronic accumulation dilemma, dimensional scaling represents a definitive frontier. The engineering design of ultra-small nanozymes ensures efficient glomerular filtration, enabling rapid renal clearance and preventing their long-term accumulation in vivo [203, 204]. Finally, developing biodegradable material systems is a key strategy for actively managing the in vivo fate of nanozymes [205]. These materials are engineered to maintain structural integrity and catalytic activity throughout the therapeutic window, followed by a controlled transition into nontoxic byproducts. The above-mentioned strategies are expected to break the trade-off between high catalytic performance and biosafety in electric field regulation, facilitating the safe realization of its significant therapeutic potential in clinical translation.

7.2 | The Ambiguity of Biological Mechanisms

The realization of precise therapy necessitates a paradigm shift from empirical trial-and-error approach to rational and predictable design. At present, the mechanistic insights into electric-field-enhanced nanozyme activity are predominantly derived from idealized DFT calculations or simplified aqueous experiments [206]. However, a profound chasm remains between these models and the intricate physiological conditions in vivo. For electric field-regulated nanozymes, catalytic outcomes are typically obtained from the confluence of multiple factors, including ROS generation, bioelectricity, thermal effects, and cavitation. For sophisticated architectures such as high-entropy alloys or heterojunctions, AC electric fields will induce highly convoluted reaction pathways [207, 208]. The variations in frequency and waveform can fundamentally alter the rate-determining steps, rendering the precise influence of the electric field difficult to predict. Due to the lack of standardized protocols and in situ characterization to distinguish and capture these disparate contributions, the understanding of the mechanisms of these processes still mainly remains at the speculative level. This opacity ultimately hinders targeted optimization and rational design for future advancements.

The integration of advanced in situ characterization techniques and artificial intelligence (AI) modeling will significantly expedite the analysis and mechanistic elucidation of these complex catalytic processes [209, 210]. These techniques can achieve nanoscale visualization of surface reconstruction and lattice deformation in nanozymes under applied electric fields. By monitoring transient valence state and coordination environment

fluctuations with a millisecond temporal resolution, researchers can track reaction sites triggered by an electric field and resolve the spatial heterogeneity of catalytic activity. These capabilities will effectively decipher the “black box” of the mechanism and provide definitive guidance for future investigations. Furthermore, by leveraging AI to perform deep learning on experimental datasets, it is explored to reveal the non-linear correlations between electric field parameters (such as frequency and waveform) and catalytic kinetics. Importantly, the elucidation of catalytic mechanisms will enable the quantitative prediction of therapeutic outcomes and the tailoring of personalized treatment regimens for individual patients.

7.3 | The Attenuation and Invasiveness of Energy Transmission

The precision of electric field-mediated regulation is determined by the accuracy of energy deposition at the designated target sites. Although direct external electric fields offer the highest controllability, they typically necessitate the implantation of electrodes, which carry a high risk of invasion and infection [211]. Moreover, deep tissues often exhibit highly uneven electric field distributions [212]. Although US-mediated piezocatalysis offers a wireless alternative solution, its efficacy is often hampered by the strong reflection and attenuation of acoustic waves by bone structures, such as the skull or ribs. This results in insufficient energy deposition at target sites, especially in intracranial diseases like glioblastoma or deep-seated visceral tumors. To overcome these depth-dependent limitations, future research may focus on real-time acoustic phase correction in complex media to ensure precise energy focusing at deep lesions. Furthermore, for long-term chronic disease management, strategies are shifting toward harvesting biomechanical energy, including heartbeats and respiration. The development of flexible implantable devices based on TENG or piezoelectric effects can convert these physiological movements into endogenous electric fields, therefore driving nanozyme activity in vivo.

In conclusion, electric-field regulated nanozymes are positioned at the nexus of nanomaterials, electrocatalysis, and precision medicine, necessitating interdisciplinary collaboration to fully harness their potential. By combining external physical modulation with intrinsic enzymatic activity, the therapeutic platforms will facilitate the transition from passive adaptation to active intervention, providing precise, controllable, and intelligent solutions for complex diseases. These advancements are poised to drive transformative progress in catalytic nanomedicine, bridging the chasm between experimental innovation and clinical translation. Ultimately, this strategy will achieve a paradigm shift from passive environmental adaptation to active, programmable, and precise therapy.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 32571629), the Liaoning Province Revitalization Talent Program (No. XLYC2503189), the Natural Science Foundation of Liaoning Province (Grant No. 2024011874-JH4/4800), and the Scientific Research

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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