

Piezoelectric-amplified sonodynamic efficiency and nanozyme activities of bismuth/cerium co-doped sodium niobate for destruction of tumors

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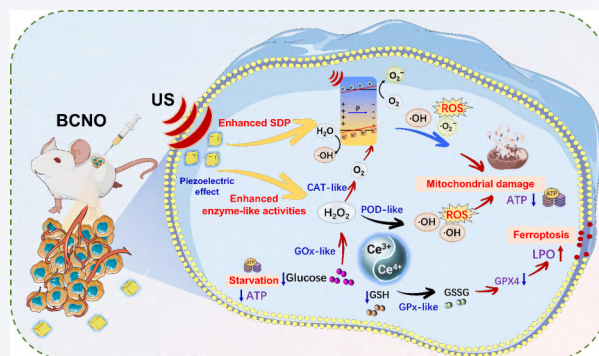
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ABSTRACT: Sonodynamic therapy and nanozyme have emerged as innovative technologies for anti-tumor therapy. Herein, we proposed a novel strategy to combination of piezoelectric-enhanced sonodynamic efficacy and enzyme-like activities for treatment of tumors. A piezoelectric material with enzyme-like activities of bismuth/cerium (Bi/Ce) co-doped sodium niobate (BCNO) was constructed. The co-doping of Bi/Ce ions in BCNO not only induced lattice distortion and bandgap reduction that remarkably enhanced piezoelectricity, but also endowed it with enzyme-like activities due to the change in valence state of Ce ions. Under irradiation of ultrasound (US), the piezoelectric effect of BCNO not only markedly amplified sonodynamic efficiency, but also facilitated the cascade reactions of glutathione peroxidase (GPx)/peroxidase (POD) and catalase (CAT)/glucose oxidase (GOx)/POD enzyme-like activities, which produced massive reactive oxygen species (ROS) for synergistic eradicating tumor cells and destructing tumors. The results demonstrated that the piezoelectric effect of BCNO caused severe oxidative stress, promoted glutathione depletion, induced ferroptosis, and interrupted the energy metabolism of tumor cells, ultimately achieving significant anti-tumor effects. This study developed a novel piezoelectric biomaterial with enzyme-like activities through a dual-ion doping strategy and provided a new solution for tumor therapy.



KEYWORDS: piezoelectric effect, sonodynamic efficacy, enzyme-like activities, cascade reaction, antitumor

1 Introduction

Tumors are among the most serious diseases that threaten human health, and are characterized by distinctive features of the tumor microenvironment (TME), including mild acidity (pH = 6.5–6.9), vascular abnormalities, inflammation, hypoxia, glycolysis dependence, and hydrogen peroxide overexpression [1–3]. The conventional treatments of tumors include radiotherapy, chemotherapy and surgery, etc., but they generally suffer from

unsatisfactory curative results or even are detrimental to the biological functions of normal cells/tissues [1, 3, 4]. Sonodynamic therapy (SDT) has emerged as one of the promising and potential approaches to tumor treatment with high efficacy as well as minimal side effects [5]. Under the irradiation of ultrasound (US), the sonosensitizers are activated, which undergo a series of redox reactions with the surrounding water (H₂O) and oxygen (O₂) to produces abundant hydroxyl radicals (·OH) as well as superoxide anions (·O₂[−]), namely reactive oxygen species (ROS) [5]. The accumulated ROS in the cytoplasm and organelles oxidize the phospholipids on cell membrane, as well as DNA and proteins inside the tumor cells, thereby leading to cell apoptosis and eventual death [6]. However, most current sonosensitizers still face challenges related to the low efficiency of ROS production for SDT and complex TME [6]. Moreover, excessive glutathione (GSH) in the TME consumes the produced ROS, thereby decreasing the efficacy of SDT [7]. As a result, it is necessary to investigate more

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efficient sonosensitizers with TME responsiveness to improve ROS production for SDT and deplete GSH in the TME for synergistic anti-tumor effects.

Recently, piezoelectric materials have garnered significant attention as a novel generation of sonosensitizers for amplifying SDT, such as barium titanate (BaTiO_3), zinc oxide, and bismuth oxychloride, etc. [8]. With US, piezoelectric materials remarkably improve the efficiency of ROS generation due to the formation of built-in electric field, which facilitates the separation and migration of electrons (e^-) and holes (h^+) for enhancing redox reactions [8]. The production of substantial amounts of ROS by piezoelectric materials has found widespread applications in tumor therapies [8, 9]. However, the effect of SDT alone on tumor treatment is still limited. Therefore, a new strategy for the combination of SDT with other approaches to completely eradicate tumors is expected to be developed. Sodium niobate (NaNbO_3 , NNO) is a piezoelectric material, which has been studied for bone repair due to its good biocompatibility [10–12]. As a sonosensitizer to amplify SDT, NNO has the problem of insufficient sonosensitivity due to the low piezoelectricity, wide bandgap, and low efficiency of carrier separation and migration [13]. Therefore, it is expected to enhance the efficiency of ROS production for NNO in SDT.

Nanozymes are a kind of nanomaterial with enzyme-like activities that possess significant advantages (e.g., low cost, good durability, high stability, easy storage, and excellent reusability) compared with natural enzymes [14]. For this reason, nanozymes have been widely applied in the biomedical field (e.g., cancer therapy, anti-inflammatory, neurological disease and disinfection) [15, 16]. Until now, many nanozymes with remarkable enzyme-like activities have been discovered, and the types of enzyme-like activities principally include oxidoreductase (e.g., peroxidase (POD), oxidase (OXD), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glucose oxidase (GOx)), and hydrolase (e.g., phosphatase) as well as nitrate reductase [14]. The majority of nanozymes have been found to have ROS production ability based on their intrinsic oxidases-like activities, such as POD- and OXD-like activities, which can be utilized for anti-tumor therapy [14]. However, in comparison with natural enzymes, nanozymes still exhibit much low bioactivities, and the applications of nanozymes for anti-tumor are still in the preliminary stage [14]. Moreover, it is still challenging to obtain a fundamental insight into the key factors that affect the enzyme-like activities. Cerium (Ce) is a rare earth element that has both valence states of Ce^{3+} and Ce^{4+} [17, 18]. The reduced state of Ce^{3+} and oxidized state of Ce^{4+} can be converted to each other, leading to the strong oxidation-reduction ability [17, 18]. For example, in acidic environment, Ce^{3+} can be oxidized to Ce^{4+} , acting as POD-like for catalyzing the conversion of hydrogen peroxide (H_2O_2) to $\cdot\text{OH}$, while the Ce^{4+} can be reduced to Ce^{3+} in alkaline environment, facilitating the decomposition of H_2O_2 to O_2 as a CAT-like nanozyme [17, 18].

Bismuth (Bi) with $6s^2$ lone-pair electrons is a potential candidate for inducing local structural distortions and improving piezoelectricity [19]. For example, both Bi-doped pyrochlore ($\text{Ca}_2\text{Nb}_2\text{O}_7$) and BaTiO_3 exhibit a significant enhancement of piezoelectricity [20, 21]. The existence of $6s^2$ lone-pair electrons is considered one of the main factors that cause the difference in ferroelectric characteristics compared to PbTiO_3 (Pb^{2+} with $6s^2$ lone-pair electrons) and BaTiO_3 (Ba^{2+} without lone-pair electrons) [22]. The doping of metal ions into piezoelectric material is an effective method to not only improve piezoelectricity but also shorten the

bandgap, which is useful for facilitating electron transfer, and thus improve the efficiency of ROS production for SDT [23]. Moreover, the doping of variable-valency metal ions into piezoelectric materials can not only increase piezoelectricity but also endow them with enzyme-like activities [24].

Herein, Bi/Ce co-doped sodium niobate (BCNO) with improved piezoelectricity and enzyme-like activities was prepared for antitumor. Under US, the piezoelectric effect of BCNO not only enhance efficiency of SDT but also improve activities of nanozymes, which produce a substantial amount of ROS ($\cdot\text{OH}$, $\cdot\text{O}_2^-$ and H_2O_2) for synergistic eradicate tumor cells both *in vitro* and *in vivo* (Scheme 1).

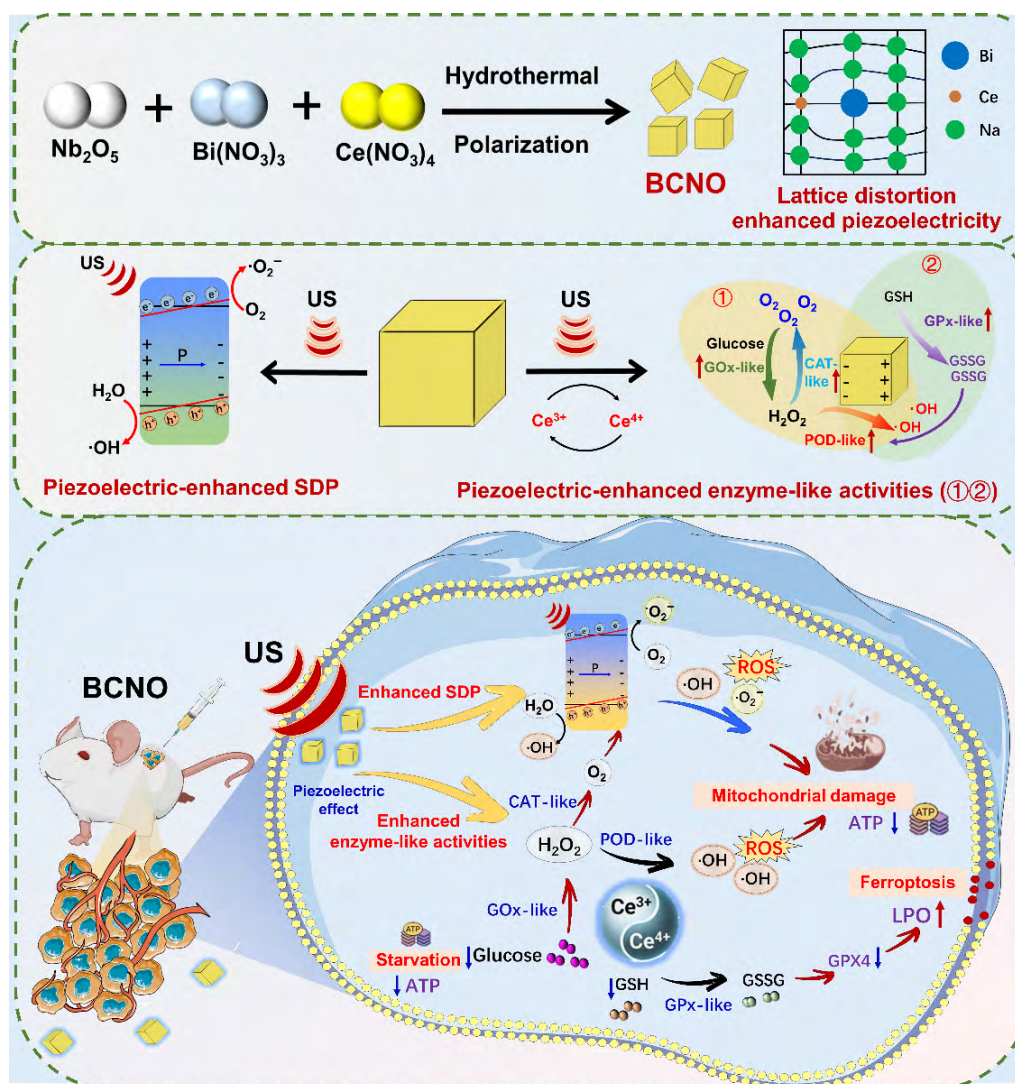
2 Results and discussion

2.1 Characterizations of BCNO

Scanning electron microscopy (SEM, Fig. S1a in the Electronic Supplementary Material (ESM)), transmission electron microscope (TEM, Figs. 1(a₁) and 1(b₁); Figs. S2(a₁) and S2(b₁) in the ESM) and dynamic light scattering (DLS) plots (Fig. S1(b) in the ESM) reveal that NNO, BNO, CNO and BCNO exhibit square-shaped morphology, with particle sizes ranging from 100 to 400 nm, and no significant differences in morphology and particle size. High-resolution TEM (HRTEM) images (Figs. 1(a₂) and 1(b₂), and Figs. S2(a₂) and S2(b₂) in the ESM) demonstrate that the lattice spacing of the (110) plane for BNO (0.398 nm), CNO (0.387 nm) and BCNO (0.397 nm) displays slight changes compared with NNO (0.391 nm). Inverse fast Fourier transform (IFFT) images (Figs. 1(a₃) and 1(b₃), and Figs. S2(a₃) and S2(b₃) in the ESM) further confirm that compared with NNO, prominent lattice distortions are observed for BNO, CNO, and BCNO. Energy dispersive X-ray spectroscopy mapping (EDS mappings, Figs. 1(a₄) and 1(b₄), and Figs. S2(a₄) and S2(b₄) in the ESM) display that the corresponding elements are distributed in NNO, BNO, CNO and BCNO, indicating the co-doping of Bi/Ce ions in BCNO.

X-ray diffractometry (XRD, Fig. 1(c)) demonstrates that the diffraction peaks at $2\theta = 22.68^\circ$ (110), 32.46° , 46.35° and 46.79° in NNO (PDF# 73-0803) exhibit slight changes in CNO (22.75° , 32.50° , 46.36° and 46.84°), BNO (22.49° , 32.22° , 46.06° and 46.46°) and BCNO (22.52° , 32.27° , 46.16° and 46.55°). Compared with NNO, no peak disappears and no new peak appears in CNO, BNO and BCNO, indicating no change in phase structure [25–27]. Magnified XRD reveals that compared with NNO (0.27°), the full width at half maximum of peak (110) for CNO (0.31°), BNO (0.35°) and BCNO (0.40°) exhibits a slight increase. Moreover, compared with NNO (31.54 nm) (Fig. S3 in the ESM), the grain sizes of BNO (27.49 nm), CNO (24.30 nm), and BCNO (21.16 nm) display a slight change, with the distortion rates of 0.12%, 0.19%, and 0.26% (Fig. 1(d)), indicating that BCNO induces obvious lattice distortion. X-ray photoelectron spectroscopy (XPS, Fig. 1(e)) reveals the presence of Bi, Ce, Na, Nb, and O elements in BCNO. XPS fitting calculation (Table S1 in the ESM) shows that the contents of Bi in BNO and BCNO are 2.04% and 2.22%, respectively, and the contents of Ce in CNO and BCNO are 1.92% and 1.89%, respectively.

High-resolution XPS of Bi 4f (Fig. 1(f)) identifies that the binding energies of Bi^{3+} (163.28 and 157.95 eV) in BNO exhibit a positive shift in BCNO (164.25 and 158.92 eV) [28]. High-resolution XPS of Ce 3d (Fig. 1(g)) reveals that the binding energies of Ce^{3+} (904.03



Scheme 1 Ultrasound-driven piezoelectric effect of bismuth/cerium co-doped sodium niobate enhances sonodynamic performance and enzyme-like activities that generate ROS for synergistic disrupting energy metabolism (glycolysis inhibition and mitochondrial damage) and boosting ferroptosis, thereby promoting tumor apoptosis.

and 885.83 eV) and Ce^{4+} (900.75 and 882.21 eV) in CNO shift to those of Ce^{3+} (903.95 and 885.25 eV) and Ce^{4+} (900.24 and 881.56 eV) in BCNO [29]. The contents of Ce^{3+} and Ce^{4+} in CNO are 35.11% and 64.89%, respectively, while those in BCNO are 42.79% and 57.21%. The electron transferred from Bi to Ce significantly alters the electronic structure of the active sites, and the change in $\text{Ce}^{3+}/\text{Ce}^{4+}$ ratio improves enzyme-like activities [30]. High-resolution XPS of Na 1s (Fig. 1(h)) shows that the binding energy of Na^+ (1070.93 eV) in NNO exhibits slight changes in CNO (1071.52 eV), BNO (1071.85 eV), and BCNO (1072.03 eV) [25]. According to the principle of ionic radius substitution, the dopant ions preferentially replace elements with similar radii [31]. Accordingly, the Na^+ sites (102 pm) in NNO are replaced by Bi^{3+} (103 pm) and Ce^{3+} (101 pm)/ Ce^{4+} (87 pm) rather than by Nb^{5+} (64 pm) [32]. Compared with NNO, the peak intensity and area of Na 1s in BNO, CNO and BCNO decrease due to the doping ions occupying the Na sites [33]. High-resolution XPS of Nb 3d (Fig. 1(i)) reveals that compared with NNO (206.75 and 209.51 eV), the binding energies of BNO (207.03 and 209.81 eV), CNO (206.94 and 209.67 eV), and BCNO (207.29 and 209.99 eV) display

slight changes caused by the dopant ions [25, 27]. Compared to NNO, there is no significant change in peak intensity and area for BNO and CNO, indicating that Bi^{3+} , Ce^{4+} and Ce^{3+} do not occupy the Nb site. Figure 1(j) reveals the schematic diagram of co-doping of Bi/Ce ions in BCNO, where the Na ions are substituted by Bi^{3+} , Ce^{4+} and Ce^{3+} ions. In short, compared with NNO, the co-doping of Bi/Ce ions does not change the phase structure but induces lattice distortion of BCNO.

2.2 Piezoelectricity and piezoelectric-amplified sonodynamic performance

Piezo-response force microscopy (PFM) of amplitude and phase maps reveals that the contrast between bright and dark regions for NNO (Fig. 2(a)) is the lowest, slightly increases for CNO (Fig. 2(b)), obviously increase for BNO (Fig. 2(c)), and exhibits the highest increase for BCNO (Fig. 2(d)), indicating excellent piezoelectricity [34]. Phase hysteresis (Figs. 2(e)–2(h)) and butterfly loop (Figs. 2(i)–2(l)) curves reveal approximately 180° phase reversal when the direction of the applied voltage changes, confirming the piezoelectricity of all samples [34, 35]. Butterfly loop curves display

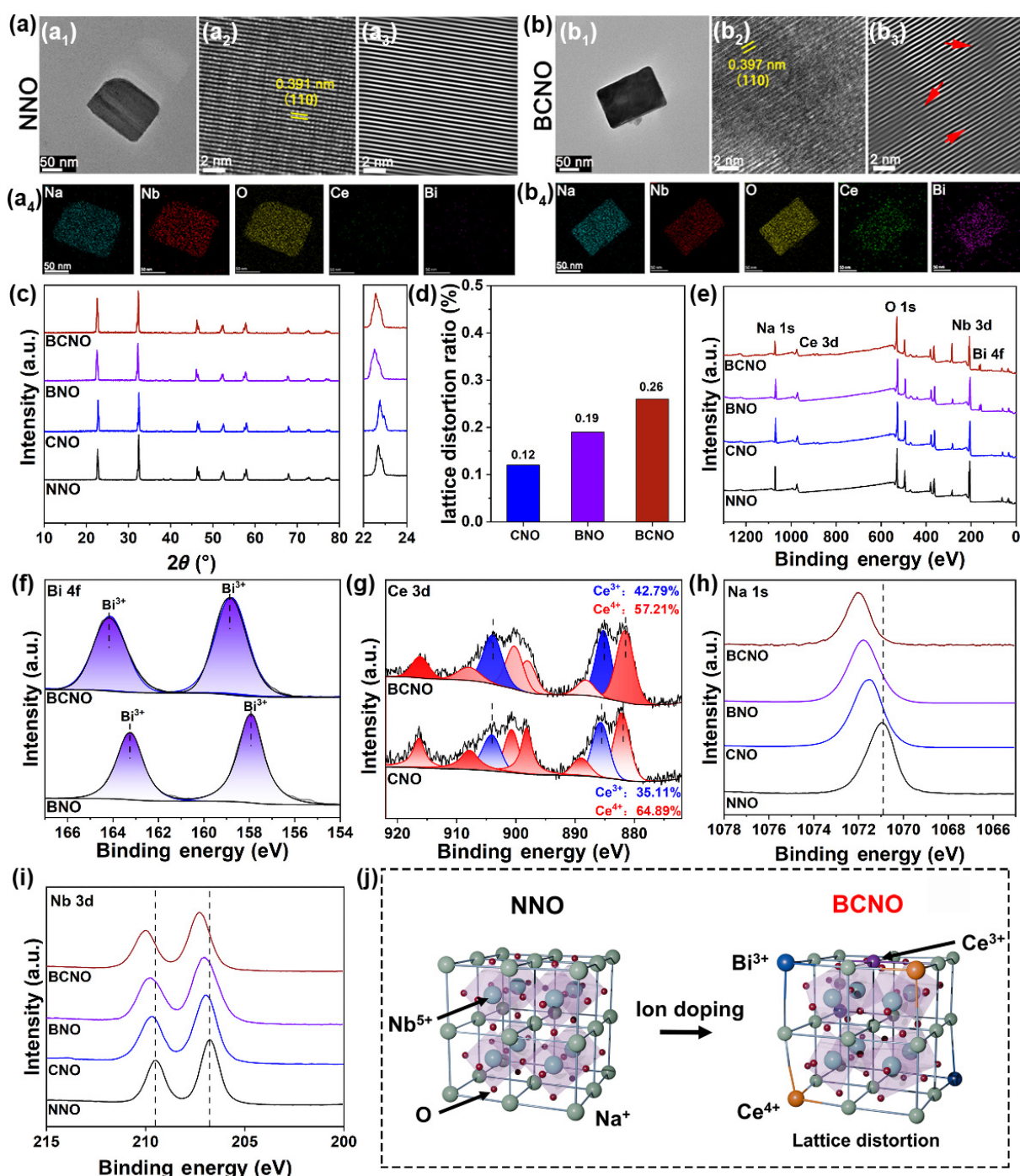


Figure 1 Morphology and structure. (a₁) and (b₁) TEM, (a₂) and (b₂) HRTEM, (a₃) and (b₃) IFFT images, and (a₄) and (b₄) EDS mapping of NNO and BCNO. (c) XRD and magnified XRD at 22°–24°, (d) Lattice distortion rate and (e) XPS of different samples. High-resolution XPS of (f) Bi 4f and (g) Ce 3d of BNO, CNO and BCNO. High-resolution XPS of (h) Na 1s and (i) Nb 3d of different samples. (j) Schematic diagrams of Bi/Ce co-doped BCNO.

that the amplitude intensity of NNO (Fig. 2(i)) is low, that of CNO (Fig. 2(j)) slightly increases, that of BNO (Fig. 2(k)) further increases, and that of BCNO (Fig. 2(l)) exhibits the highest, confirming the improvement in piezoelectricity. Piezoelectric coefficient (d_{33}) is one of the key properties of piezoelectric materials, reflecting the conversion efficiency from mechanical to electrical energy [36]. Compared with NNO (21.62 pm/V), the d_{33} of CNO (37.57 pm/V) slightly increases, while that of BNO (70.23 pm/V) obviously enhances, indicating that the doping of Bi

is better than Ce ions for improving piezoelectricity. Compared with BNO, the d_{33} of BCNO (109.21 pm/V) significantly increases, confirming a remarkable improvement in piezoelectricity. The co-doping of Bi/Ce ions induces lattice distortion in BCNO, which increases the non-centrosymmetric structure and affects dipole moments, resulting in a significant improvement of piezoelectricity [37, 38].

The band gap (E_g) of sonosensitizers is one of the key parameters for improving sonodynamic performance (SDP) in the production of ROS under US [39]. Tauc plots (Fig. 3(a)) reveal that compared

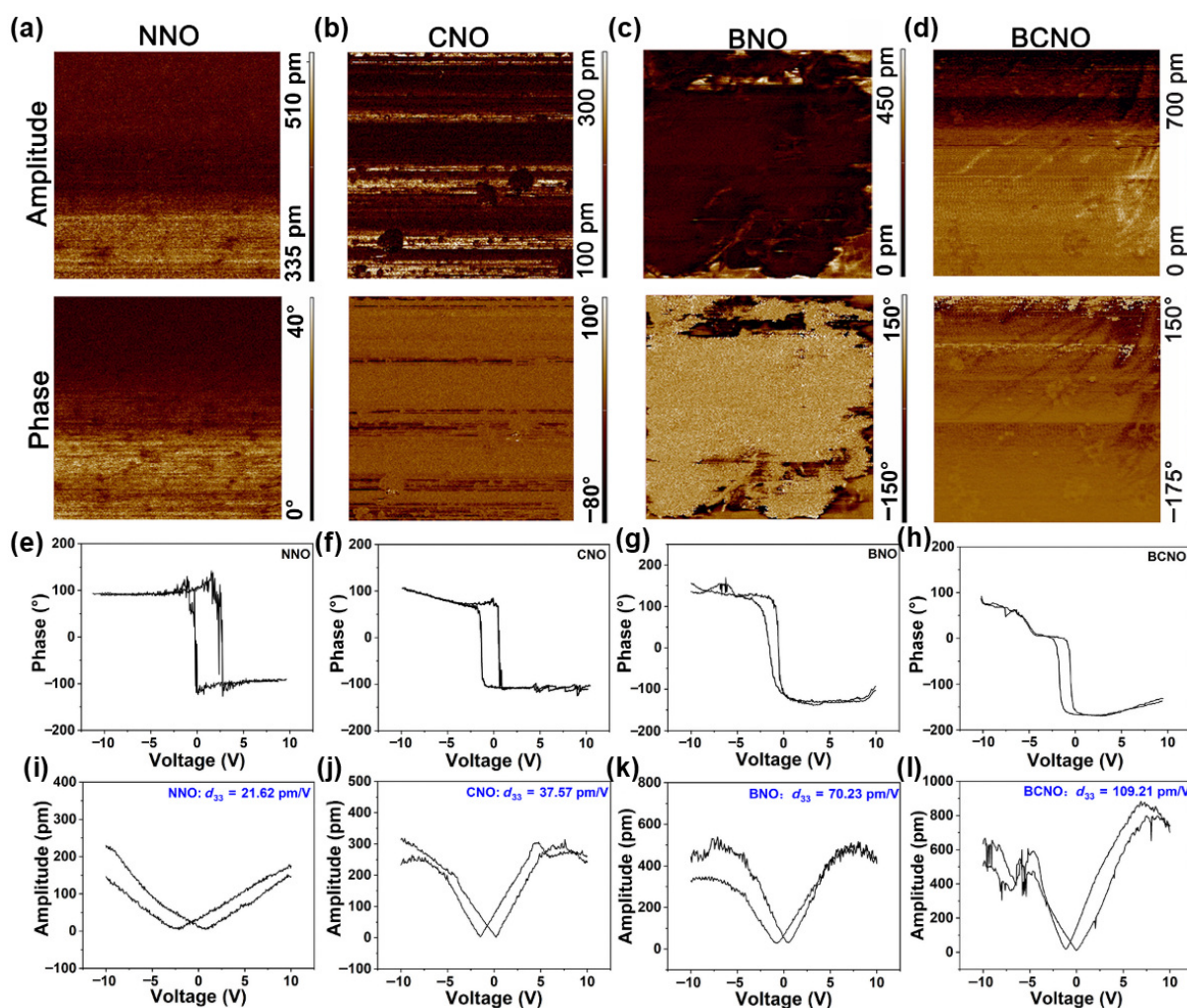


Figure 2 Piezoelectricity. PFM of (a)–(d) amplitude and phase maps, and (e)–(h) phase hysteresis and (i)–(l) butterfly loop curves of different samples.

with NNO (3.24 eV), CNO (2.97 eV) and BNO (2.89 eV), the E_g of BCNO (2.76 eV) obviously reduces, which is favorable to accelerate the separation and migration of charge carriers under US stimulation, and more carriers participate in redox reactions to generate more ROS [39, 40]. Valence Band-XPS (VB-XPS) spectra (Figs. 3(b)–3(e)) reveal that compared with NNO (+2.50 eV), the valence band (E_{VB}) of CNO (+2.07 eV), BNO (+2.27 eV) and BCNO (+2.10 eV) reduces. According to the formula ($E_{CB} = E_g - E_{VB}$) [38], the conduction band (E_{CB}) of NNO, BNO, CNO and BCNO are -0.74 , -0.62 , -0.90 , and -0.66 eV, respectively. Electrochemical impedance spectroscopy (EIS) (Fig. 3(f)) shows that compared with NNO, BNO and CNO, the arc radius of BCNO is the smallest, demonstrating the lowest resistance to electron transfer and thus improving separation of the e^- - h^+ pairs [38]. The transient piezo-current spectroscopy curves (I - t curves, Fig. 3(g)) demonstrates that with US, compared with NNO ($0.40 \mu\text{A}/\text{cm}^2$), CNO ($0.66 \mu\text{A}/\text{cm}^2$) and BNO ($0.91 \mu\text{A}/\text{cm}^2$), the ultrasonic current density of BCNO ($1.19 \mu\text{A}/\text{cm}^2$) is the highest, indicating the improvement of carrier generation and migration of e^- - h^+ pairs [38].

As shown in Figs. 3(h) and 3(j), with US, the absorbance of methylene blue (MB) and 1,3-diphenylisobenzofuran (DPBF) for the samples decreases (NNO > CNO > BNO > BCNO), indicating the improvement in the production of $\cdot\text{OH}$ and $\cdot\text{O}_2^-$. The production of $\cdot\text{OH}$ and $\cdot\text{O}_2^-$ for BCNO is the highest, implying the

significant improvement of SDP. Electron spin resonance (ESR, Figs. 3(i) and 3(k)) further demonstrates that the signal intensities of $\cdot\text{OH}$ and $\cdot\text{O}_2^-$ for BCNO are the strongest, implying excellent SDP. Figure 3(l) shows that, as the US intensity increases, the absorbance of rhodamine B (Rh B) for BCNO gradually decreases, indicating the improvement in ROS production. Figure 3(m) indicates that the absorbance for BCNO gradually decreases with the increase of US irradiation time ($1.5 \text{ W}/\text{cm}^2$), indicating the increase of ROS generation with time. In short, the generation of ROS by BCNO is the highest, suggesting excellent SDP. Figure 3(n) demonstrates the mechanism of the US-driven piezoelectric effect enhanced SDP of BCNO. The co-doping of Bi/Ce ions reduces the E_g of BCNO, which decreases the electron transition energy and increases the carrier concentration [39]. Driven by US, the formation of built-in electric field in BCNO not only promotes the separation and migration of e^- - h^+ pairs, but also induces energy band bending. This enables more carriers to migrate to the material surface, thereby participating in redox reactions and thus enhancing ROS generation [8]. The E_{VB} of BCNO is more positive than that of $\text{H}_2\text{O}/\cdot\text{OH}$ (+2.01 eV), allowing the catalytic production of $\cdot\text{OH}$ from H_2O , while the E_{CB} of BCNO is more negative than that of $\text{O}_2/\cdot\text{O}_2^-$ (-0.33 eV), allowing the catalytic production of $\cdot\text{O}_2^-$ from O_2 [39]. Therefore, the piezoelectric effect of BCNO effectively boosts the SDP for the generation of ROS.

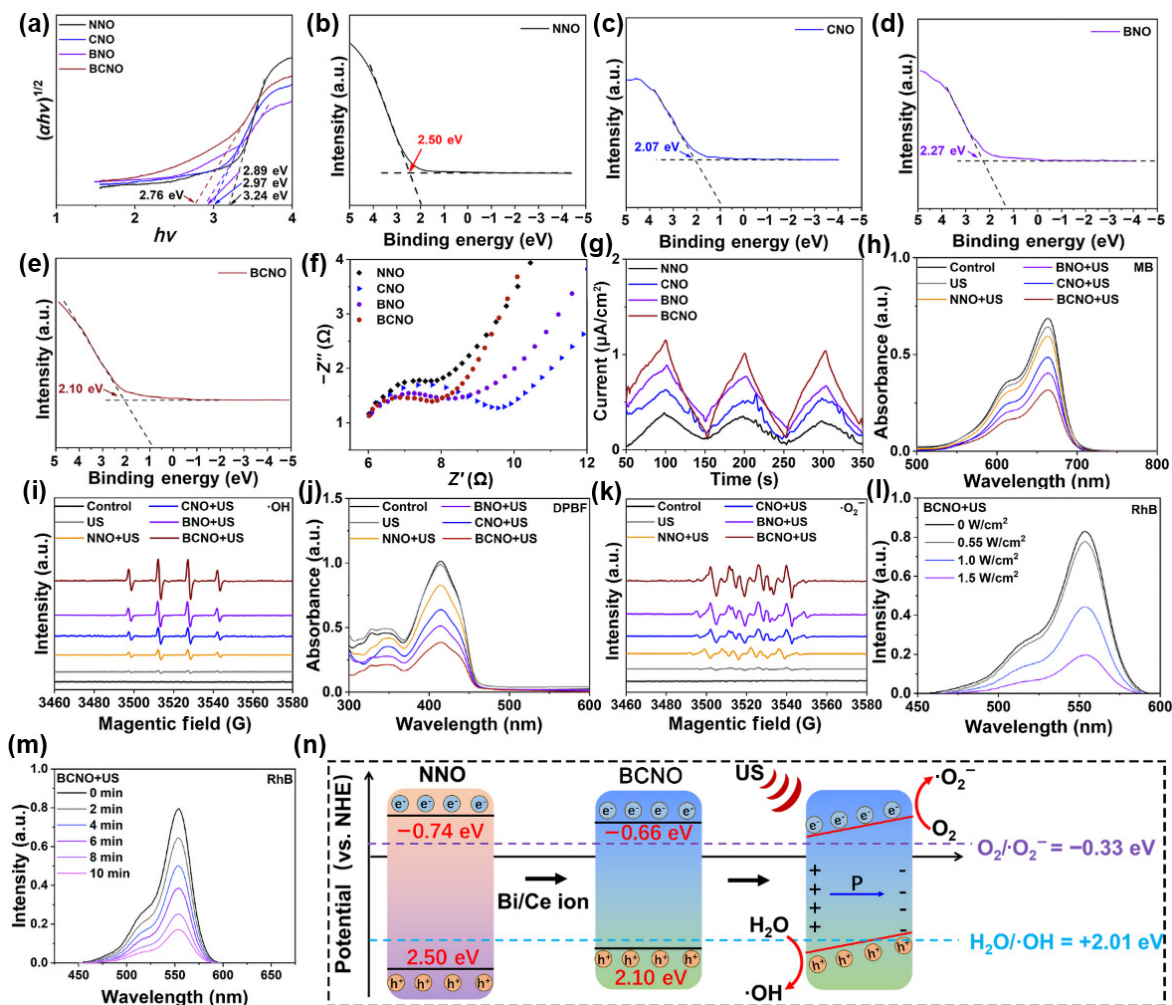


Figure 3 Sonodynamic performance (SDP): (a) Tauc plots, (b)–(e) VB-XPS spectra, (f) EIS and (g) $I-t$ curve of different samples; UV-vis-NIR absorption spectra of (h) MB and (j) DPBF, and ESR of (i) $\cdot\text{OH}$ and (k) $\cdot\text{O}_2^-$ for different groups; UV-vis-NIR absorption spectra of Rh B with different power of (l) US and (m) time for BCNO; (n) schematic diagrams of mechanism on piezoelectric-amplified SDP of BCNO.

2.3 Piezoelectric-amplified enzyme-like activities

Figure 4(a) reveals that at pH = 6.5, the absorbance values for CNO and BCNO are significantly elevated than those of the controls, implying the POD-like activity for production of $\cdot\text{OH}$ (CNO < BCNO). With US, the production of $\cdot\text{OH}$ for BCNO further increases, indicating piezoelectric-amplified POD-like activity. Figure 4(b) reveals that the absorbance of BCNO increases with pH decreasing, confirming that the POD-like activity is pH-sensitive and effective in an acidic environment. Figure 4(c) displays that at pH = 6.5, the maximum reaction velocity (V_m , 11.63×10^{-8} M/s) increases, while the Michaelis-Menten constant (K_m , 35.11 mM) decreases for BCNO+US compared with BCNO (9.38×10^{-8} M/s, 58.69 mM), indicating the improvement in affinity to the substrate (H_2O_2). Figure 4(d) reveals that at pH = 6.5, the V_m (11.7×10^{-8} M/s) increases, while K_m (1.45 mM) decreases for BCNO+US compared with BCNO (7.4×10^{-8} M/s, 1.65 mM), indicating enhanced substrate affinity (3,3',5,5'-tetramethylbenzidine, TMB) [41]. The improvements in the affinity of BNCO to the substrates is ascribed to the piezoelectric effect, which accelerates electron transfer to promote the valence state transition of Ce ions, thereby reducing the binding energy between nanozymes and substrates [42, 43].

Figure 4(e) shows that the O_2 concentrations for CNO ($\Delta\text{O}_2 = 3.4 \pm 0.2$ mg/L) and BCNO ($\Delta\text{O}_2 = 3.0 \pm 0.2$ mg/L) are obvious, indicating CAT-like activity. With US, the O_2 concentration for BCNO ($\Delta\text{O}_2 = 4.1 \pm 0.1$ mg/L) further increases, demonstrating piezoelectric-amplified CAT-like activity. Figure 4(f) reveals that the O_2 concentration for BCNO increases with the increase in pH, and at pH = 7.4, O_2 concentration is highest (4.5 ± 0.1 mg/L), confirming that the CAT-like activity is pH-sensitive and effective in an alkaline environment. Figure 4(g) shows that at pH = 6.5, the V_m (0.54 mg/(L·min)) increases, while K_m (48.06 mM) decreases for BCNO+US compared with BCNO (0.37 mg/(L·min), 56.24 mM), indicating an improvement in affinity to the substrate (H_2O_2).

The presence of GSH in tumor cells decreases the efficacy of ROS in anti-tumor therapy, and GPx-like activity can deplete GSH for inhibiting tumor cell growth [1]. Figure 4(h) shows that compared with NNO and BNO, the absorbances of GSH for CNO and BCNO obviously decrease, indicating GPx-like activity (CNO < BCNO). With US, the GPx-like activity for BCNO further increases, indicating piezoelectric-amplified GPx-like activity. Figure S4(a) in the ESM shows that the GPx-like activity of BCNO increases with rising of pH, with neutral conditions being more favorable for improving the GPx-like activity. ESR (Fig. 4(i))

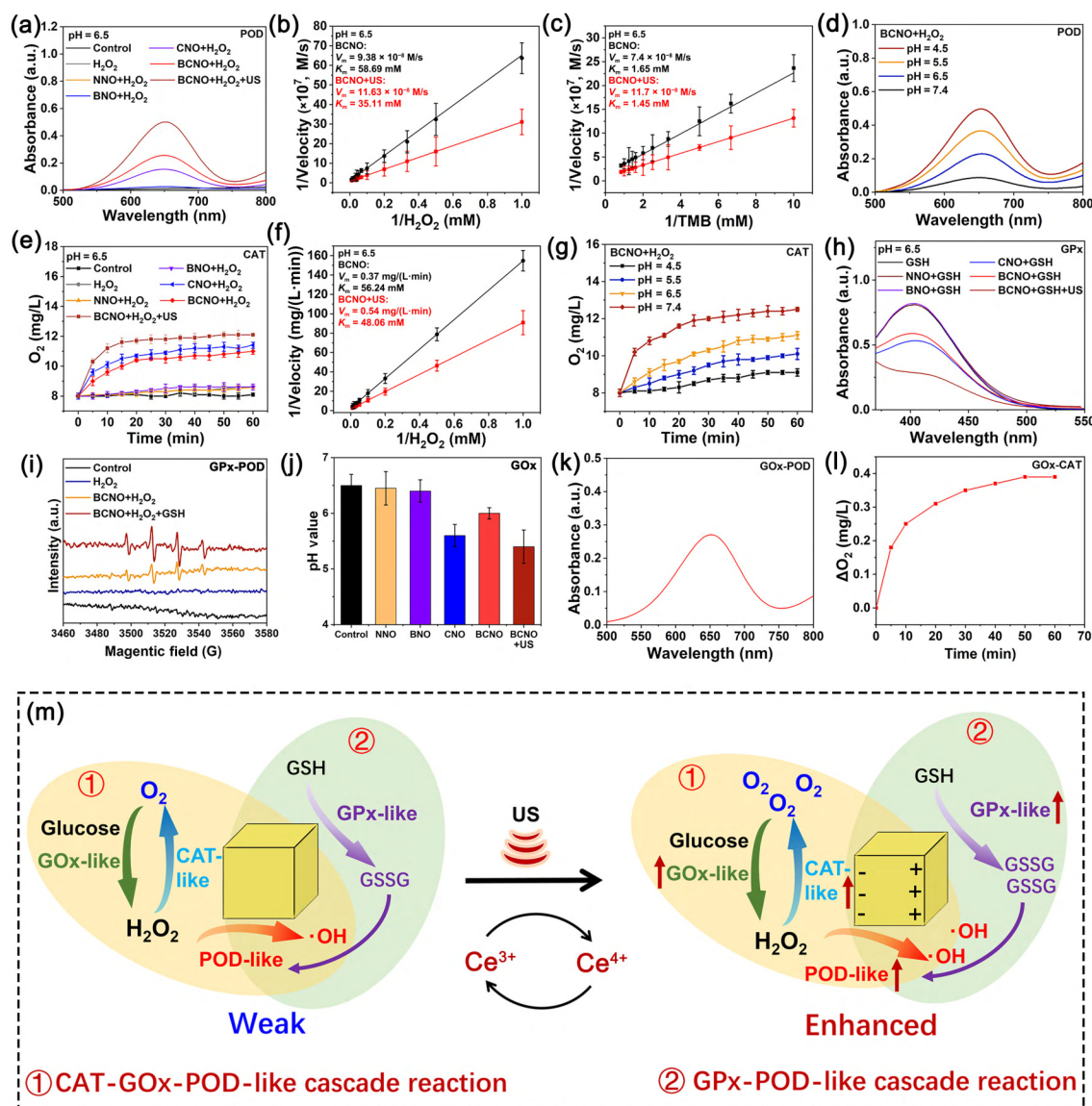


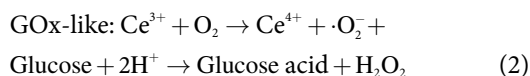
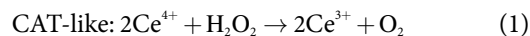
Figure 4 Enzyme-like activities: UV-Vis-NIR absorption spectra of (a) TMB for different groups and (d) various pH; Lineweaver-Burk plots of BCNO and BCNO+US, with (b) H_2O_2 and (c) TMB; O_2 production for (e) different groups and (g) various pH; (f) Lineweaver-Burk plot of BCNO and BCNO+US with H_2O_2 ; (h) absorption spectra of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) for different groups; (i) ESR spectra of production of $\cdot\text{OH}$ for GPx-POD cascade reaction; (j) pH of glucose solution with different groups; (k) UV-Vis-NIR absorption spectra of TMB for BCNO in glucose solution; (l) production of O_2 of BCNO in glucose solution; (m) schematic diagram of US-driven piezoelectric-amplified enzyme-like activity of BCNO, $n = 3$.

demonstrates that the signal peak of $\cdot\text{OH}$ for $\text{BCNO} + \text{H}_2\text{O}_2 + \text{GSH}$ is higher than that for BCNO, indicating an improvement in $\cdot\text{OH}$ generation by GPx-POD-like cascade reaction.

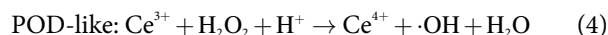
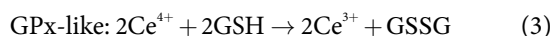
Glucose in cancer cells can be converted to H_2O_2 and glucuronic acid by GOx-like enzymes for tumor starvation therapy [17, 44]. Moreover, H_2O_2 is a key substrate for POD-like and CAT-like activities in tumor cells [17, 18]. A timely supply of H_2O_2 is essential for killing tumor cells. Figure 4(j) shows that compared with NNO and BNO, the pH of glucose solution decrease for CNO and BCNO, indicating their GOx-like activity. With US, the pH of BCNO further decrease, indicating piezoelectric-amplified GOx-like activity. Figure S4(b) in the ESM demonstrates that the OD value decreases with decreasing pH, confirming that the acidic condition is more favorable for improving the GOx-like activity of BCNO. Figures 4(k) and 4(l) demonstrate that the H_2O_2 produced by the

GOx-like activity is further utilized by the GOx/CAT-like and GOx/POD-like cascade reactions of BCNO for the production of $\cdot\text{OH}$ and O_2 in glucose solution. Figure 4(m) reveals the two cascade reactions of BCNO through valence change of Ce ions:

① CAT/GOx/POD-like cascade reaction: CAT-like activity converts H_2O_2 to O_2 (1), which then converts to $\cdot\text{O}_2^-$ via GOx-like activity during glucose oxidation, regenerating H_2O_2 (2) [16].



② GPx/POD-like cascade reaction: GPx-like activity converts GSH to glutathione disulfide (GSSG) (Ce^{4+} to Ce^{3+}) (3), and POD-like activity changes H_2O_2 to $\cdot\text{OH}$ (Ce^{3+} to Ce^{4+}) (4) [45].



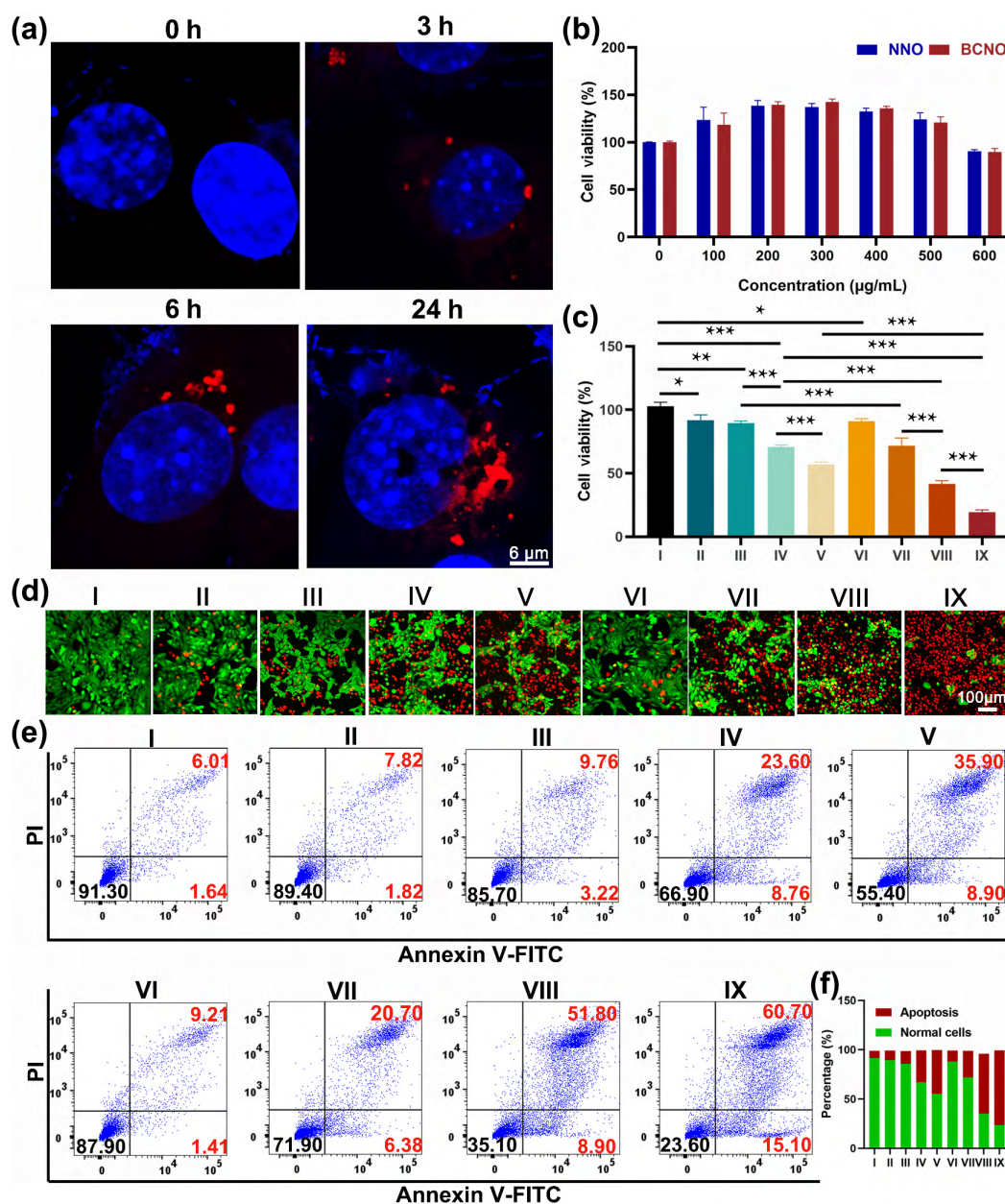
The piezoelectric effect of BCNO induces more electron migration that participates in the redox reaction, thereby enhancing CAT/GOx/POD-like and GPx/POD-like cascade reactions for the production of a large amount of ROS.

Figure S5 in the ESM shows that the sonodynamic efficiencies (Figs. S5(a) and S5(b) in the ESM) and the enzyme-like activities (Figs. S5(c)–S5(f) in the ESM) remain robust after 14 days of incubation, demonstrating that the function of BCNO is stable throughout the therapeutic window.

2.4 Anti-tumor activity *in vitro*

2.4.1 Apoptosis of Sarcoma osteogenic-2 (Saos-2) cells

Figure 5(a) reveals that the red fluorescence of Rh B-labeled BCNO particles around the nucleus of Saos-2 cells gradually increases with time, indicating the cellular phagocytosis of BCNO particles. Figure 5(b) reveals that viabilities exhibit high cytocompatibility toward bone-marrow-derived mesenchymal stromal cells (BMSCs), indicating no cytotoxicity of NNO and BCNO at concentrations up to 500 µg/mL. Figure 5(c) reveals that compared with BCNO, the viability of Saos-2 cells ($57.08\% \pm 1.80\%$) for BCNO with H_2O_2 significantly decrease due to the ROS production by enzyme-like activities, while the viability ($41.64\% \pm 2.52\%$) for BCNO with US obviously decrease due to ROS production by piezoelectric-



I: Control II: H_2O_2 III: NNO IV: BCNO V: BCNO+ H_2O_2 VI: US VII: NNO+US VIII: BCNO+US IX: BCNO+ H_2O_2 +US

Figure 5 Cell uptake and anti-tumor evaluation: (a) Confocal laser scanning microscope (CLSM) images of cellular phagocytosis of BCNO at different time; (b) cytotoxicity of NNO and BCNO for BMSC; (c) viability of Saos-2 cells; (d) CLSM images of calcein-AM/PI co-staining of Saos-2 cells; (e) flow cytometry images and (f) quantitation of apoptosis of Saos-2 cells, $n = 3$. Statistical significance was defined as $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.

amplified SDP. With H_2O_2 and US, the viability ($19.28\% \pm 1.90\%$) of BCNO significantly reduces, demonstrating an excellent anti-tumor effect because piezoelectric-amplified SDP and enzyme-like activities produce a large amount of ROS for killing tumor cells. Calcein-AM/PI co-staining (Fig. 5(d)) shows that BCNO with either H_2O_2 or US, results in fewer live (green) cells and more dead (red) cells compared with BCNO alone, indicating an anti-tumor effect. With H_2O_2 and US, the number of dead cells for BCNO further increases, implying excellent anti-tumor effect. Flow cytometry images (Fig. 5(e)) and quantitation (Fig. 5(f)) indicate that, compared to BCNO, with H_2O_2 or US alone, the apoptosis of Saos-2 cells for BCNO significantly increases. With H_2O_2 and US, BCNO triggers a higher rate of programmed cell apoptosis, with a cell survival rate of 23.60%, confirming good antitumor effect. In summary, the US-driven piezoelectric-amplified SDP and enzyme-like activities of BCNO produce a large amount of ROS for collaboratively killing tumor cells, exhibiting an excellent anti-tumor effect.

2.4.2 Induction of ferroptosis of Saos-2 cells

The production of ROS and the depletion of GSH trigger ferroptosis in tumor cells [46]. The GSH is usually overexpressed in tumor tissues, which depletes ROS to satisfy the redox homeostasis required for tumor cell growth, thereby weakening the efficacy of killing tumor cells [1]. Figures 6(a) and 6(c) reveal that compared with other controls, the intracellular GSH is significantly depleted for BCNO due to ROS production and GPx-like activity. With

H_2O_2 , the GSH for BCNO is remarkably reduced due to ROS production by the GPx/POD-like cascade. With US, GSH for BCNO reduces due to ROS production by piezoelectric-amplified SDP and GPx-like activity. With H_2O_2 and US, the consumption of GSH for BCNO is the highest due to ROS production by piezoelectric-amplified SDP and GPx/POD-like cascade reaction. Figures 6(e) and 6(f) display that, compared with BCNO, with H_2O_2 or US alone, the concentration of GSH for BCNO obviously decreases (GSSG increases). With H_2O_2 and US, the concentration of GSH for BCNO further decreases (GSSG further increases), indicating significant consumption of GSH.

Downregulation of glutathione peroxidase 4 (GPX4) activity and accumulation of lipid peroxide (LPO) are key pathways in ferroptosis [46]. Figure 6(g) shows that compared with the controls, the GPX4 expression for BCNO decreases, and further decreases for BCNO+ H_2O_2 . With H_2O_2 and US, the GPX4 expression for BCNO significantly decreases due to the piezoelectric-amplified SDP and enzyme-like activities that generate a large amount of ROS for the downregulation of GPX4 expression. Figures 6(b), 6(d), and 6(h) display that compared to BCNO, with H_2O_2 or US alone, the liperfluor and malondialdehyde (MDA) concentrations for BCNO significantly increase. With H_2O_2 and US, the LPO and MDA for BCNO further increase, indicating that BCNO+ H_2O_2 +US significantly induces LPO in Saos-2 cells. In summary, the US-activated piezoelectric effect of BCNO enhances SDP and the GPx/POD-like cascade, for more ROS production, leading to the

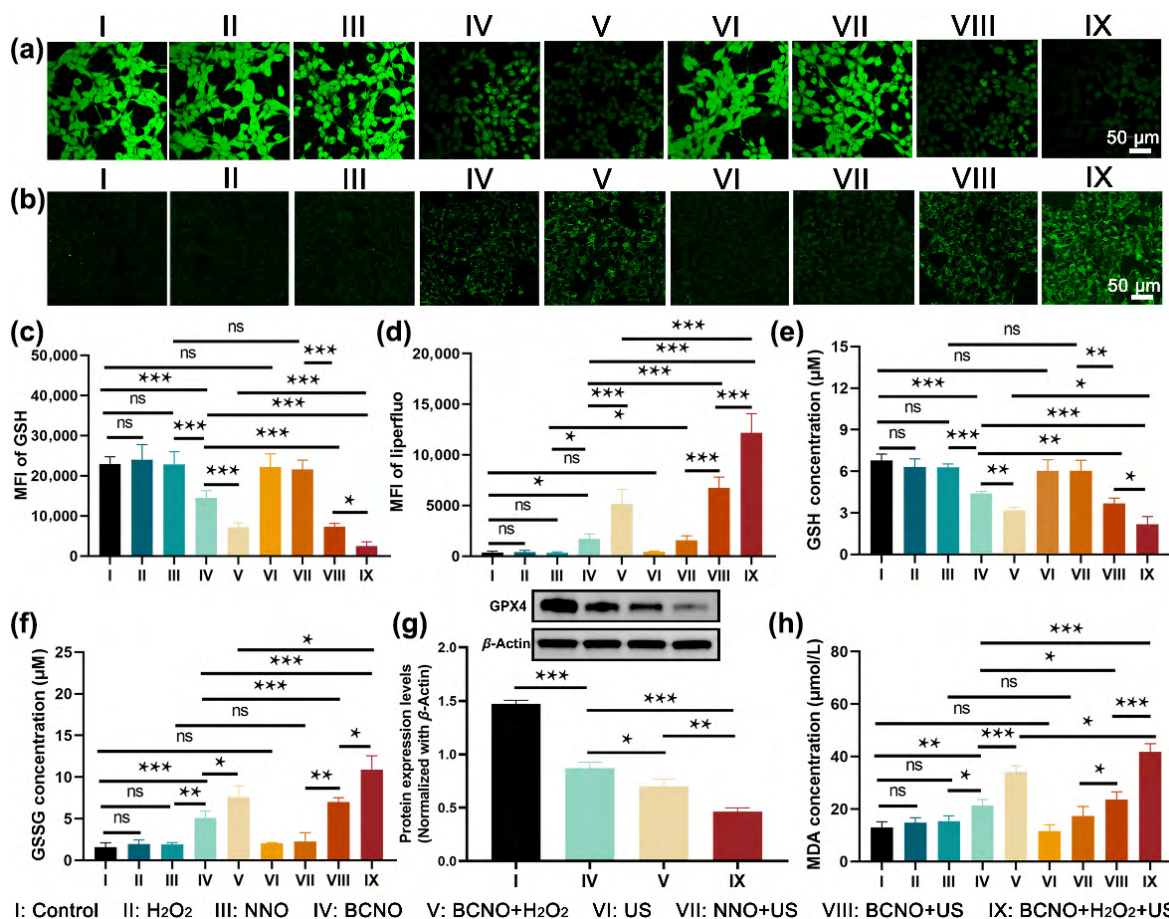


Figure 6 Ferroptosis: CLSM images of (a) GSH, (b) Liperfluor staining, and (c) and (d) the relative quantification; (e) GSH and (f) GSSG concentrations; (g) Western blotting bands of GPX4 and quantitation, and (h) MDA concentration of Saos-2 cells for different groups, $n = 3$, ns: no significance. Statistical significance was defined as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

downregulation of GPX4 expression and accumulation of LPO, and thereby triggering the ferroptosis of tumor cells.

2.4.3 Mitochondrial damage of Saos-2 cells

The substrates (O_2 and H_2O) for ROS generation by US are predominant, and GOx-like activity consumes endogenous glucose, which also requires the participation of O_2 [5, 17]. However, the microenvironment of tumor cells is hypoxic, which decreases the effect of SDP and interferes with the glycolytic pathway [2]. Figures 7(a) and 7(d) show that compared with BCNO, the intracellular hypoxia is significantly relieved for BCNO+ H_2O_2 due to the generation of O_2 by CAT-like activity, and the hypoxia for BCNO+ H_2O_2 +US further decreases due to the H_2O_2 supply and piezoelectric-amplified CAT-like activities for the generation of more O_2 . Figures 7(b) and 7(e) demonstrate that compared with BCNO, the ROS level for BCNO+ H_2O_2 obviously increases due to enzyme-like activity, while that for BCNO+US significantly increases due to piezoelectric-amplified SDP. The ROS level for BCNO+ H_2O_2 +US further increases due to the piezoelectric-amplified SDP and enzyme-like activities.

Elevated levels of exogenous ROS trigger mitochondrial remodeling, including mitochondrial fragmentation (such as mitochondrial membrane potential (MMP) and bioenergetic collapse (reduced adenosine triphosphate (ATP) synthesis, respiratory chain inactivation, etc.), thereby inducing mitochondrial-

mediated apoptosis in tumor cells [45, 47, 48]. Figures 7(c) and 7(f) show that, compared with BCNO, the JC-1 monomer/aggregate fluorescence ratio for BCNO increases with H_2O_2 or US, indicating the decrease in MMP. With H_2O_2 +US, the ratio for BCNO further increases, indicating a severe decrease of MMP due to the piezoelectric-amplified SDP and enzyme-like activity that produces ROS for damaging the mitochondria of Saos-2 cells.

ATP, the energy source of tumor cells, can also be generated by glycolysis, whereas GOx-like activity inhibits glycolysis through the consumption of glucose, which prevents energy metabolism, thereby promoting apoptosis of tumor cells [48, 49]. Figure 7(g) shows that compared with the controls, the glucose concentration for BCNO slightly decreases because of low GOx/CAT-like activity. With H_2O_2 , a notable depletion of glucose is observed for BCNO due to the improvement of GOx/CAT-like cascade reaction. With US, the glucose concentrations for BCNO further decrease due to the piezoelectric-amplified GOx/CAT-like activities. With H_2O_2 and US, the glucose concentration for BCNO further decreases because of the synergistic effects of H_2O_2 supply and piezoelectric-amplified GOx/CAT-like cascade reaction for the consumption of glucose. Figure 7(h) displays that compared with BCNO, the ATP level for BCNO with H_2O_2 obviously decreases due to mitochondrial damage by ROS and glycolysis inhibition caused by GOx/CAT-like cascade reaction to inhibit ATP synthesis. With US, the ATP level for BCNO obviously decreases due to mitochondrial damage

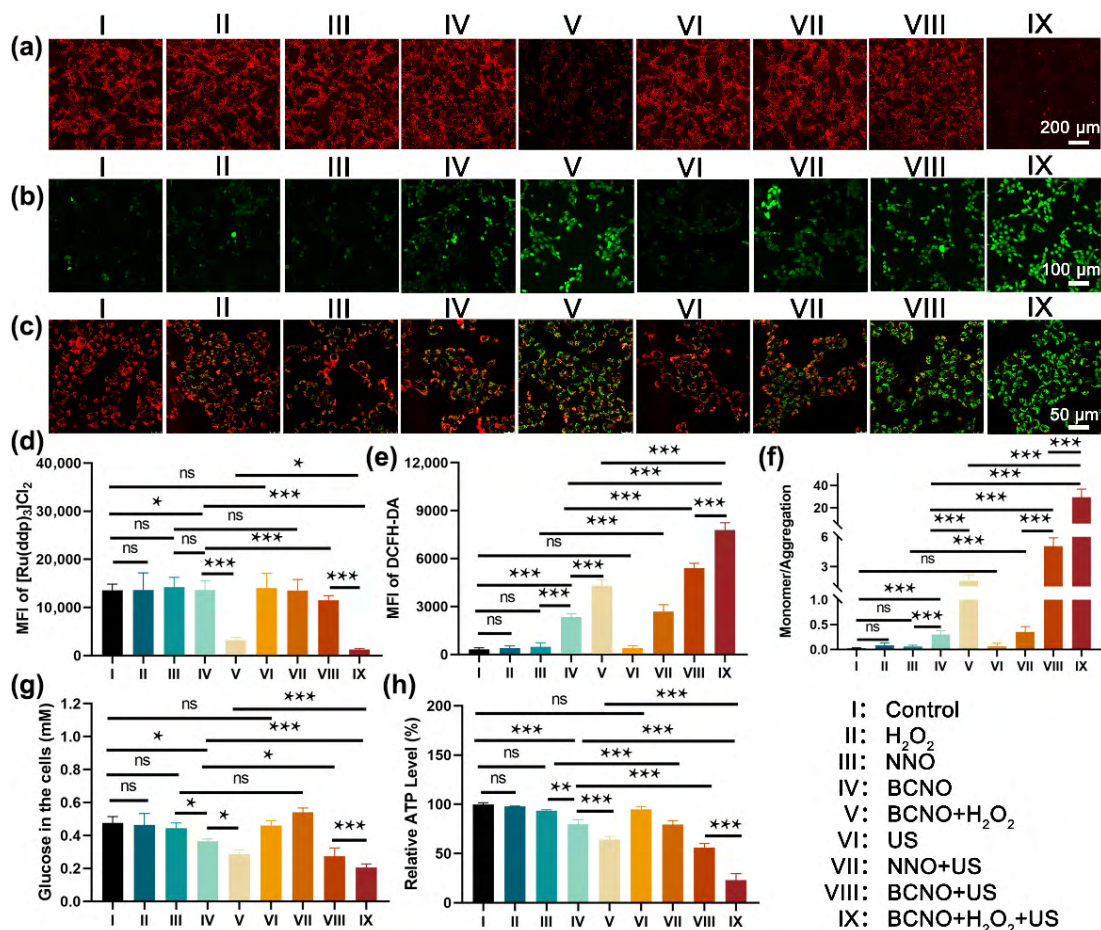


Figure 7 Oxidative stress and energy metabolism disorders: CLSM images of (a) [Ru(ddd)₃]Cl₂, (b) DCFH-DA, and (c) JC-1 staining, and (d)–(f) quantification of Saos-2 cells for different groups; (g) intracellular glucose concentration and (h) ATP levels of Saos-2 cells, $n = 3$. ns: no significance. Statistical significance was defined as $P < 0.05$, $*P < 0.01$, and $**P < 0.001$.

caused by ROS generated by piezoelectric-amplified SDP and the GOx/CAT-like cascade reaction, which inhibits ATP synthesis. With H_2O_2 and US, the ATP level for BCNO significantly decreases because of the synergistic effect of H_2O_2 supply and piezoelectric-amplified SDP and enzyme-like activities that produce more ROS for the destruction of a large number of mitochondria, as well as the inhibition of glycolysis for the decrease of ATP synthesis.

2.5 Mechanism of anti-tumor

For RNA-sequencing of BCNO+ H_2O_2 +US and Control, the volcano plot (Fig. 8(a)) shows that of the detected 6955 expressed differentially expressed genes (DEGs), 4958 genes are up-regulated, while 1977 genes are down-regulated. Figure 8(b) reveals that terms exhibit significant enrichments related to transmembrane

transporter activity, RNA polymerase I/II transcription repressor complex, preribosome, DNA-binding transcription repressor activity, negative regulation of cell growth/glycolytic process, lipid metabolic process, ATP-dependent regulation, glutathione catabolic process, and response to O_2 levels, indicating that BCNO+ H_2O_2 +US interacts with cells via membrane transporters, and significantly impacts energy metabolism and DNA/RNA transcription. Figure 8(c) reveals that BCNO+ H_2O_2 +US significantly impacts the oxidative stress (HIF-1 signaling pathway), ferroptosis-related pathways (glutathione metabolism, ferroptosis), energy supply (oxidative phosphorylation, glycolysis/gluconeogenesis), and apoptosis-related signaling pathways (p53, cell cycle, TNF, Hippo), and immune-related signaling pathways (TGF- β , IL-17, NF- κ B) of the tumor cells [50–52]. Figure 8(d) reveals that BCNO+ H_2O_2 +US

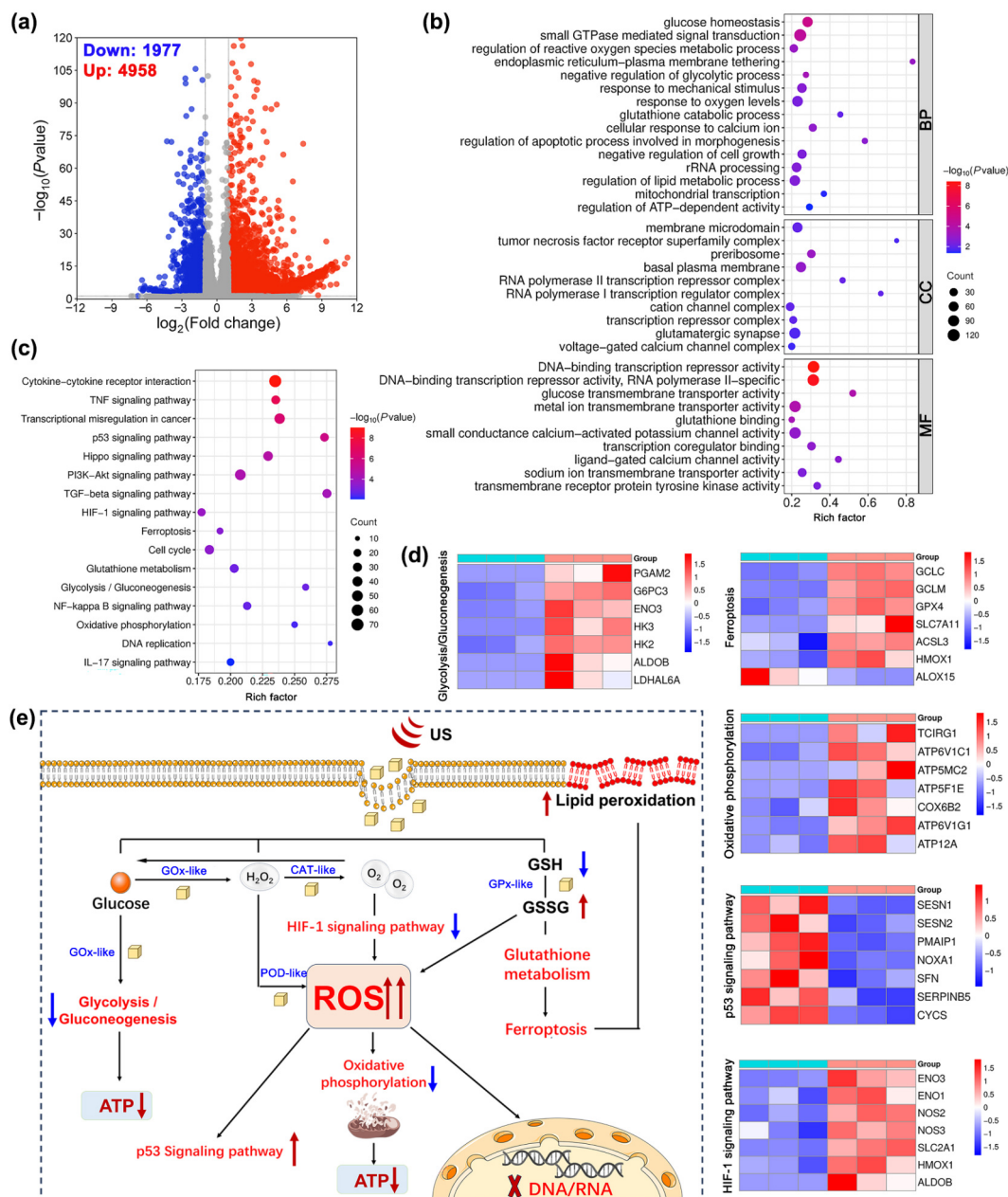


Figure 8 Anti-tumor mechanism: (a) Volcano plot; (b) GO and (c) KEGG enrichment; (d) heatmaps of related genes of glycolysis/gluconeogenesis, ferroptosis, oxidative phosphorylation, p53, HIF-1, TNF signaling pathway, oxidative phosphorylation and ferroptosis; (e) anti-tumor mechanism of BCNO+ H_2O_2 +US vs. Control, $n = 3$.

significantly upregulates p53 signaling pathway-related genes, downregulates genes related to glycolysis/gluconeogenesis, and oxidative phosphorylation (inhibiting energy metabolism), ferroptosis, and HIF-1 related pathway (alleviating the hypoxic microenvironment). Figure 8(e) reveals the antitumor mechanism: The piezoelectric effect of BCNO effectively enhances SDP and enzyme-like activity that produces a large amount of ROS, which triggers oxidative stress for inducing ferroptosis and mitochondrial damage, and impeding DNA/RNA replication of tumor cells, thereby promoting apoptosis. Moreover, BCNO inhibits glycolysis through GOx-like activity, disrupting the energy supply for promoting death of tumor cells.

2.6 Anti-tumor activity of BCNO *in vivo*

Hematoxylin and eosin (H&E) staining images (Fig. 9(k)) show that the tumor tissues of the controls are relatively dense, while those of BCNO display some signs of apoptosis. Especially, with US, BCNO displays typical signs of apoptosis or necrosis, such as solidification, nucleolysis and extensive cytoplasmic leakage. Ki-67 is an important indicator for assessing the proliferation of tumor cells [53]. Figure 9(l) shows that BCNO inhibits tumor cell proliferation, indicating an antitumor effect. With US, the proliferation of tumor cells for BCNO is significantly inhibited, indicating the best anti-tumor effect *in vivo*. Figures 10(a) and 10(e) reveal that compared with the controls, the apoptosis of tumor cells for BCNO significantly increases, indicating an anti-tumor effect. With US, the apoptosis for BCNO further enhances, confirming the best anti-tumor effect *in vivo*. The hypoxic microenvironment of tumor tissue impairs the therapeutic efficacy of SDP, and hypoxia-inducible factor 1- α (HIF-1 α) is the key indicator for assessing the hypoxia of tumor cells [54]. Figures 10(b) and 10(f) reveal that compared to the controls with hypoxia, the expression of HIF-1 α for BCNO and BCNO+US obviously decreases due to the O₂ production, indicating mitigated intratumoral hypoxia, thereby sensitizing the SDP. Figures 10(c) and 10(g) show that compared with the controls, the ROS level for BCNO obviously increases. With US, the ROS level for BCNO further enhances. Figures 10(d) and 10(h) demonstrates that compared with the controls, the expression of GPX4 for BCNO is obviously down-regulated due to the decrease of GSH caused by ROS. With US, the expression of GPX4 for BCNO is significantly down-regulated due to the further decrease of GSH caused by ROS. In summary, as a piezoelectric acoustic sensitizer, BCNO displays great potential for high-efficiency anti-tumor therapy.

3 Conclusions

Through a simple strategy of dual-element doping engineering, the Bi/Ce co-doped sodium niobate (BCNO) with improved piezoelectricity and enzyme-like activities was constructed for treatment of tumors. The co-doping of Bi/Ce ions induced the lattice distortion and bandgap reduction of BCNO, thereby enhancing piezoelectricity and sonodynamic efficiency. Moreover, BCNO exhibits enzyme-like activities of cascade reactions (GPx/POD-like and CAT/GOx/POD-like) due to the doping of Ce ions with optimized ratio of Ce³⁺/Ce⁴⁺. With US, the piezoelectric effect of BCNO markedly amplified both sonodynamic efficiency and enzyme-like activities in cascade reactions, thereby producing large amounts of ROS ($\cdot$ OH, H₂O₂, and $\cdot$ O₂⁻) for synergistically promoting the apoptosis of tumor cells. The significant

improvement in killing tumor cells by BCNO was attributed to synergistic depletion of GSH, induction of ferroptosis, inhibition of glycolysis, and mitochondrial dysfunction. The results confirmed that the piezoelectric-enhanced sonodynamic efficiency and enzyme-like activities of BCNO induce substantial tumor cell damage by severe oxidative stress, activation of the ferroptosis pathway, and disruption of cellular energy metabolism networks. This study offers a novel strategy to develop piezoelectric materials with enzyme-like activities for eradicating tumor cells and destroying tumors both *in vitro* and *in vivo*, and thereby exhibiting promising potential for tumor therapy.

4 Experimental

4.1 Reagents and chemicals

Niobium oxide (Nb₂O₅) was purchased from Shanghai Xiaohuang Nanotechnology Co., Ltd. Bismuth(III) nitrate pentahydrate (Bi(NO₃)₃·5H₂O, 99%), sodium hydroxide (NaOH, 97%), cerium (IV) nitrate (Ce(NO₃)₄, 99.9%), Rh B, MB, DPBF, and cobalt(II) chloride (CoCl₂) were purchased from Shanghai Macklin Biochemical Technology Co., Ltd. 5,5'-Dithiobis-(2-nitrobenzoic acid) (DTNB), 5,5-Dimethyl-1-pyrroline N-oxide (DMPO), tris (4,7-diphenyl-1,10-phenanthroline) ruthenium (II) dichloride ([Ru(dpp)₃]Cl₂) were purchased from Aladdin Biochemical Technology Co., Ltd. TMB was purchased from Shanghai Zhonghe Chemical Technology Co., Ltd. GSH was purchased from Shanghai Kaiwei Chemical Technology Co., Ltd. BMSCs and Saos-2 cells were purchased from Wuhan Procell Life Sciences Co., Ltd. Ultrasound diagnostic instrument (WED-100) was purchased from Shenzhen Welld Medical Electronics Co., Ltd.

4.2 Preparation of samples

The Bi/Ce-doped NaNbO₃ (BCNO) was prepared by mixing Nb₂O₅ (1.0 g), Bi(NO₃)₃·5H₂O (0.089 g) and Ce(NO₃)₄ (0.088 g) in 50 mL NaOH solution (8 mol/L) at ionic molar ratio (Nb:Bi:Ce = 94:3:3) and stirred for 2 h. The solution was reacted in a stainless steel hydrothermal reactor lined with polytetrafluoroethylene at 160 °C for 12 h. Subsequently, the product was removed, centrifuged (8000 r/min, 5 min) washed several times with distilled water and ethanol. The product was sonicated for 30 min and supernatant was collected, which was subsequently centrifuged (8000 r/min, 5 min), and the product was dried at 60 °C for 12 h. As controls, NaNbO₃ (NNO), 3% Bi-doped NaNbO₃ (BNO) and 3% Ce-doped NaNbO₃ (CNO) were prepared by the same method. Prior to use, the samples were polarized by corona polarization.

4.3 Characterization of samples

4.3.1 Physicochemical properties

The morphology, particle size, elemental distribution, interplanar spacing, chemical composition and E_{VB} of the samples were analyzed by SEM (Hitachi S-4800, Japan), TEM (JEOL JEM-2100F, Japan) and XPS (Thermo Scientific K-alpha, USA). Crystal structures were analyzed by XRD (D/max2550VB/PC, Japan), and grain size and lattice distortion rate were determined using the Scherrer equation and Williamson-Hall analysis [55]. The E_g of the samples is calculated according to the Kubelka-Munk (K-M) equation based on the UV-vis-DRS spectra (Lambda 950, USA) [38]. EIS and $I-t$ curve of the samples were characterized by

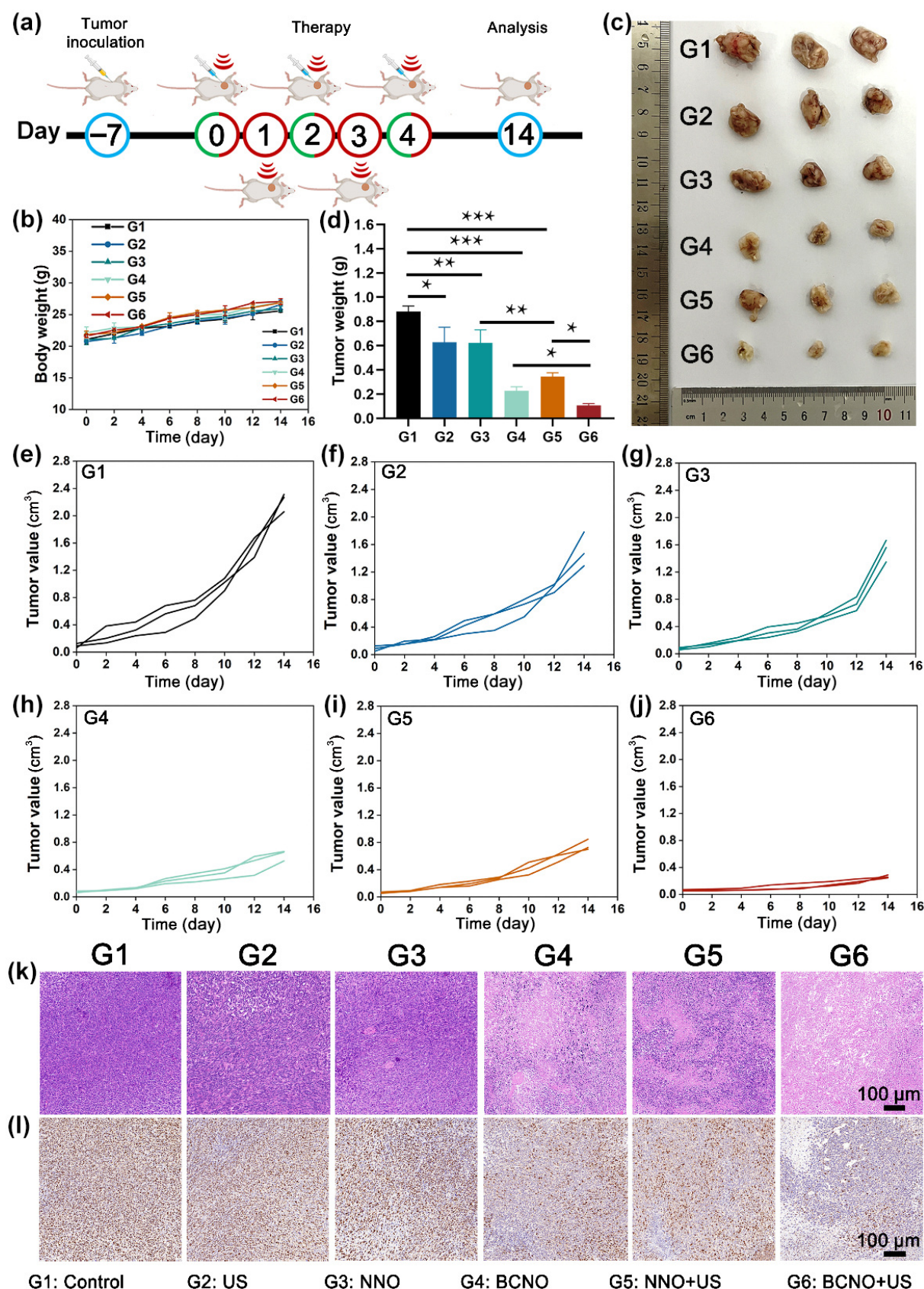


Figure 9 Anti-tumor evaluation *in vivo*: (a) Diagram of process for tumor treatment of mice; changes of (b) body weight of mice, (c) photos of tumors, (d) average weight of tumors, and (e)–(j) changes of tumors volumes of mice within 14 days; (k) H&E and (l) Ki-67 staining images of tumor sections for different groups, $n = 6$. Statistical significance was defined as $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.

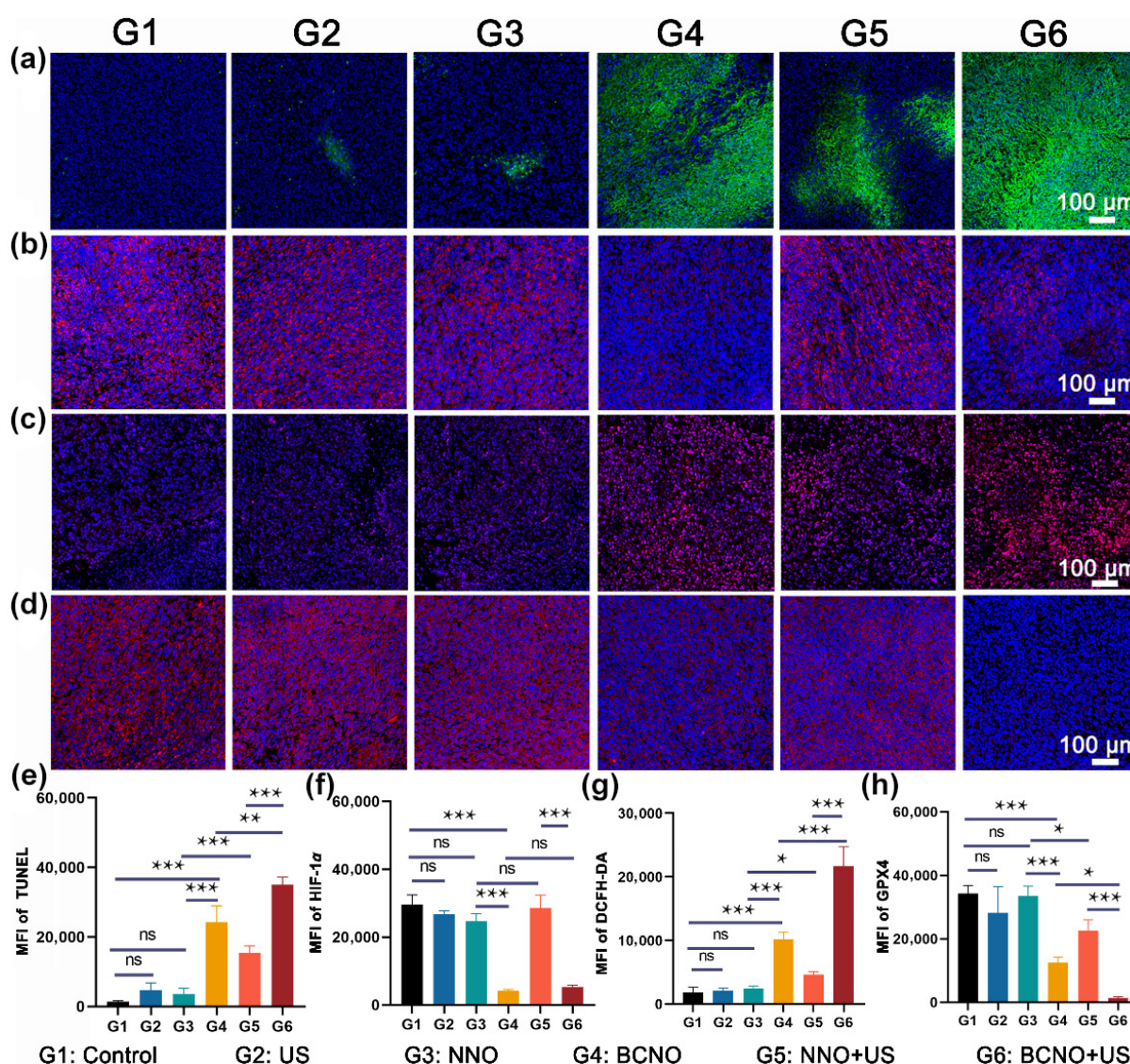


Figure 10 Anti-tumor evaluation *in vivo*: CLSM images of (a) terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL), (b) HIF-1 α , (c) DCFH-DA and (d) GPX4, and (e)–(h) the relative quantification of tumor sections for different groups, $n = 6$, ns: no significance. Statistical significance was defined as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

electrochemical workstation (CHI660E, China). Butterfly loop, phase hysteresis curve, and corresponding phase and amplitude maps are measured using PFM (NTEGRA, Russia) with applied voltage ranging from -10 to $+10$ V. d_{33} was calculated through corresponding slope of the butterfly loop [56].

4.3.2 Detection of extracellular ROS

The sample (5 mg) was dispersed in 10 mL MB ($\cdot\text{OH}$) or DPBF ($\cdot\text{O}_2^-$) solution (5 mg/L) or Rh B solution (10 mg/L). After US irradiation (1.5 W/cm 2 , 10 min, 50% duty cycle, 1 MHz), the supernatant was analyzed using UV-Vis-NIR spectrometer (Lambda 950, USA), and $\cdot\text{OH}$ and $\cdot\text{O}_2^-$ signals were captured by ESR (EMX-8/2.7, USA) with DMPO solution (1 M).

4.3.3 Determination of enzyme-like activities

POD-like activity: 5 mg sample was dispersed in 10 mL TMB solution (1.2 mM, pH = 4.5, 5.5, 6.5, 7.4) with 30 mM H $_2$ O $_2$. After reacting for 10 min with/without US irradiation (1.5 W/cm 2 , 50% duty cycle, 1 MHz). The supernatant was analyzed using

UV-vis-NIR spectrometer. The maximum reaction velocity (V_m) and Michaelis-Menten constant (K_m) were obtained by varying the concentrations of TMB and H $_2$ O $_2$ and were calculated using the Lineweaver-Burk equation [57]. CAT-like activity: 25 mg sample was dispersed in 50 mL H $_2$ O $_2$ solution (100 mM, pH = 4.5, 5.5, 6.5, 7.4). Dissolved oxygen content was recorded every 10 min with/without US irradiation (1.5 W/cm 2 , 10 min, 50% duty cycle, 1 MHz) using the dissolved oxygen analyzer (JPB-607A, China), for a total monitoring period of 60 min. V_m and K_m were obtained by varying the concentration of H $_2$ O $_2$. GPx-like activity: 5 mg sample was dispersed in 10 mL GSH solution (100 μ M, pH = 4.5, 5.5, 6.5, 7.4). After reacting for 3 h with/without US (1.5 W/cm 2 , 10 min of US/60 min, 50% duty cycle, 1 MHz), the solution was centrifuged. After that, DTNB solution (3 mg/mL) was added to the supernatant and react for 1 min, and analyzed using UV-vis-NIR spectrometer. GPx/POD-like activity: 5 mg sample was dispersed in 10 mL GSH solution (100 μ M, pH = 6.5) with 30 mM H $_2$ O $_2$, after reacting for 20 s, the $\cdot\text{OH}$ signal was collected by ESR. GOx-like activity: 10 mM samples were dispersed in glucose (100 mM, pH = 4.5, 5.5, 6.5, 7.4)

solution and reacted for 1 h with/without US (1.5 W/cm², 10 min, 50% duty cycle, 1 MHz). The initial and final pH of solutions were determined using pH meter. The glucose concentration under different pH was measured using glucose colorimetric assay kit (GOD/POD Method) (Beyotime, China). GOx/POD/CAT-like activity: 10 mM BCNO was dispersed in glucose (100 mM) solution with 1.2 mM TMB and reacted for 1 h. The supernatant was analyzed using UV-vis-NIR spectrometer, and dissolved oxygen content was recorded by dissolved oxygen analyzer. For stability testing, BCNO was immersed in PBS (pH = 6.5) solution for varying time (days 0, 1, 7, 14). The specific procedure is as described above.

4.4 Antitumor properties *in vitro*

Supplemented with 10% fetal bovine serum and 1% Penicillin/Streptomycin, the Saos-2 cells were cultured (with 5% CO₂ in a 37 °C incubator) using Dulbecco's modified Eagle's medium (DMEM). Medium was changed every 2 days. BMSC were cultured using the same method with alpha minimal essential medium (αMEM) medium. The Saos-2 cells were seeded in 24-well plates (1 × 10⁴ cells/well), and co-cultured with samples for 24 h after cell attachment. For H₂O₂-related groups, H₂O₂ (100 μM) was added to the medium. For US-related groups, US parameters were 1.5 W/cm² for 3 or 5 min, 50% duty cycle, 1 MHz. After different treatments, cells were further cultured for 6 h to conduct different tests. The concentrations of NNO and BCNO are 500 μg/mL (except for cytotoxicity).

Cellular uptake: After Saos-2 cells were co-cultured with Rh B-labeled BCNO for 0, 3, 6, and 24 h, the cells were fixed with 4% paraformaldehyde and stained with 4',6-diamidino-2-phenylindole (DAPI) staining (Biosharp, China), and observed by CLSM (LEICA TCS SP8, Germany). Cytotoxicity: Fresh medium containing BCNO with different concentrations (0, 100, 200, 300, 400, 500 μg/mL) was replaced for 24 h after cell attachment. Cell viabilities were calculated according to the instructions of cell counting kit-8 (Beyotime, China) [58]. Apoptosis: After different treatments and co-cultured for another 6 h, cell viability calculation was performed as the cytotoxicity assay. Cell Live/death staining (Beyotime, China) was tested by Calcein-AM/PI cell viability/cytotoxicity assay kit (Yeasen, China) and observed by CLSM. Apoptosis was determined by flow cytometry (BD lsrfortessa, USA) after cells co-culturing with the Annexin V-FITC/7-AAD cell apoptosis detection kit (Yeasen, China) and the data were analysed by FlowJo software.

Intracellular glucose consumption was measured by glucose assay kit with O-toluidine (Beyotime, China), and ATP analysis was performed by ATP luminescent cell viability assay kit (Beyotime, China). ROS generation was captured by CLSM after 30 min 2',7'-dichlorodihydrofluorescein diacetate (10 μM, DCFH-DA, Beyotime, China) staining. Intracellular O₂ production: After cell adhesion, CoCl₂ solution (500 μM) was used to induce chemical hypoxia. Then, the fresh medium containing samples was replaced and co-cultured for 24 h. After different treatments and co-cultured for another 6 h, cells were stained for 45 min with [Ru(DPP)₃]Cl₂ reagent (10 mg/mL, 10 μL) and washed, and then observed with CLSM.

Ferroptosis detection: Before being observed by CLSM, the cells were stained for 30 min using Thioltracker™ Violet (20 μM) (Thermo Fisher, USA). The intracellular GSH consumption was quantitatively determined by GSH and GSSG assay kit (Beyotime, China). For MMP, the cells were stained for 30 min with

mitochondrial membrane potential assay kit with JC-1 (Beyotime, China) and observed by CLSM. For LPO analysis, the cells were stained with liperfluo reagent (5 μM) (Dojindo, Japan) for 30 min, and then observed by CLSM and quantitatively analyzed with MDA assay kit (Beyotime, China). Western blot analysis of GPX4: Saos-2 cells were seeded into 6-well plates (5 × 10⁵ cells/well). After different treatments and co-cultured for another 6 h, the cells were collected and lysed, and Western blotting was performed to quantify GPX4 protein levels. β-actin was used as the internal reference protein. RNA sequencing: The RNA sequencing of lysed cells was performed by Servicebio (Wuhan, China), and untreated cells were used as the control.

4.5 Antitumor properties *in vivo*

The 6–8 week-old 36 female BALB/c mice were subcutaneously injected with 2 × 10⁶ cells (100 μL) K7M2-WT cells. When the tumor volume grew to 80–100 mm³, the model was successfully established.

After modeling, the mice were randomly divided into 6 groups: (1) Control, (2) US, (3) NNO, (4) BCNO, (5) NNO+US, (6) BCNO+US. Different particles (3 mg/kg, 100 μL) were injected into the tumor on days 0, 2, and 4. On days 0, 1, 2, 3, and 4, the tumor was irradiated with US (1.5 W/cm², 5 min). The weight of the mice and volume of the tumor ($V = (\text{width}^2 \times \text{length})/2$) were recorded every 2 days. On day 14, all mice were anesthetized and dissected. The tissues of hearts, livers, spleens, lungs and kidneys were collected for H&E staining. Tumor tissues were collected for H&E staining, Ki-67 immunohistochemical staining, and TUNEL, HIF-1α, DCFH-DA and GPX4 immunofluorescence staining.

4.6 Statistical analysis

Each experiment was performed at least three independent replicates ($n \geq 3$). Quantitative analysis of relative fluorescence intensity of CLSM images using ImageJ. All data were analyzed by two-way ANOVA or one-way ANOVA using GraphPad Prism 8 software and Origin 2018, and expressed as mean ± standard deviation (SD). Statistical significance was defined as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

Electronic Supplementary Material: Supplementary material (further details of SEM, particle size, TEM, nanozyme-like activity, biosafety and atomic percent of different samples) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94908708>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and/or the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contribution statement

S. Y. X.: Writing – original draft, writing – review & editing, validation, methodology, investigation, formal analysis, data curation, conceptualization. Y. Y.: Writing – review & editing, validation, investigation, formal analysis, visualization. W. Y. L.: Investigation, formal analysis. X. T. W.: Investigation, formal analysis. J. W.: Writing – review & editing, methodology, supervision, resources, data curation, project administration, funding acquisition, conceptualization. F. Z.: Writing – review & editing, methodology, conceptualization, methodology, resources. G. W. L.: Writing – review & editing, methodology, conceptualization, resources, funding acquisition.

Informed consent

Not applicable.

Ethics statement

The animal experiments were performed following the guidelines of Experimental Animal Ethics Committee of East China University of Science and Technology (approval number: ECUST-2024-148). All the animal experiments complied with relevant guidelines of the Chinese government and regulations for the care and use of experimental animals.

Use of AI statement

None.

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