Bactericidal effects and accelerated wound healing using \( \text{Tb}_4\text{O}_7 \) nanoparticles with intrinsic oxidase-like activity

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**Abstract**

**Background:** Nanomaterials that exhibit intrinsic enzyme-like characteristics have shown great promise as potential antibacterial agents. However, many of them exhibit inefficient antibacterial activity and biosafety problems that limit their usefulness. The development of new nanomaterials with good biocompatibility and rapid bactericidal effects is therefore highly desirable. Here, we show a new type of terbium oxide nanoparticles (\( \text{Tb}_4\text{O}_7 \) NPs) with intrinsic oxidase-like activity for in vitro and in vivo antibacterial application.

**Results:** We find that \( \text{Tb}_4\text{O}_7 \) NPs can quickly oxidize a series of organic substrates in the absence of hydrogen peroxide. The oxidase-like capacity of \( \text{Tb}_4\text{O}_7 \) NPs allows these NPs to consume antioxidant biomolecules and generate reactive oxygen species to disable bacteria in vitro. Moreover, the in vivo experiments showed that \( \text{Tb}_4\text{O}_7 \) NPs are efficacious in wound-healing and are protective of normal tissues.

**Conclusions:** Our results reveal that \( \text{Tb}_4\text{O}_7 \) NPs have intrinsic oxidase-like activity and show effective antibacterial ability both in vitro and in vivo. These findings demonstrate that \( \text{Tb}_4\text{O}_7 \) NPs are effective antibacterial agents and may have a potential application in wound healing.

**Keywords:** \( \text{Tb}_4\text{O}_7 \) nanoparticles, Oxidase, Reactive oxygen species, Antibacterial, Wound healing

**Background**

Wound infection is an important cause of poor wound healing and its treatment often requires the use of antibiotics [1, 2]. However, excessive use of antibiotics may lead to the development of antibiotic-resistant bacteria, and may also cause side effects on human health, such as gastrointestinal disturbances. In recent years, developments in nanomaterial technology have provided an opportunity to develop novel antimicrobial agents. Due to the diversity in mechanisms of action against bacteria, bacterial cells are less likely to develop antibacterial resistance compared to existing antibiotics [3–5]. However, most of these nanomaterials have application limitations, such as cytotoxicity, not biocompatible for human use, and environmental concerns.

Nanozymes are nanomaterials that catalyze the same reactions originally catalyzed by natural enzymes in biological systems [6–8]. Over the past several years, a wide variety of nanomaterials, such as noble metals [9–11], metal oxides [12–14], and carbon nanomaterials [15–18], have been explored as potential nanozymes. Based on their intrinsic enzyme-like activity, several nanozymes have been used in antibacterial applications [19–23]. For instance, platinum nanomaterials have shown effective antibacterial activity in the presence of hydrogen peroxide.
perrhydroxide (H$_2$O$_2$) [24]. The antibacterial activity of these nanozymes are attributed primarily to their oxidase- and peroxidase-like activities that catalyze the production of hydroxyl radicals (·OH) in the presence of exogenous H$_2$O$_2$ and enhance the cellular levels of reactive oxygen species (ROS) within bacteria cells. Fang et al. also showed that palladium nanomaterials with oxidase- and peroxidase-like activities displayed effective antibacterial activity in the presence of H$_2$O$_2$ [25]. Although many reported enzyme-like nanomaterials have been proposed as novel antibacterial agents, the high price and persistence in living tissues are still important issues. Moreover, the application of H$_2$O$_2$ in human wound disinfection is harmful to healthy tissue and may delay wound healing [26].

Terbium oxide nanoparticles (Tb$_4$O$_7$ NPs) have been extensively used as precursors for the synthesis of lanthanide nanophosphors and superconductor materials [27, 28]. For example, Tb$_4$O$_7$ complexed with reduced graphene oxide composite exhibit typical green emission of terbium ions as well as the blue self-luminescence of graphene [28]. In addition, it has been found that Tb$_4$O$_7$ NPs can be used as analytical reagents for food analysis [29]. Compared with noble metal nanomaterials, Tb$_4$O$_7$ NPs are easier to synthesize and are less expensive. However, a review of scientific literature was unable to find any studies that described the enzyme-like activity of Tb$_4$O$_7$ NPs and their applications as antibacterial agents. In this paper, we show that Tb$_4$O$_7$ NPs have an intrinsic oxidase-like activity at acidic pH values, as they quickly oxidize a series of organic substrates in the absence of H$_2$O$_2$. We then demonstrate the relationship between the oxidase-like property of Tb$_4$O$_7$ NPs and their antibacterial activity with in vitro studies. Finally, the effects of Tb$_4$O$_7$ NPs on wound disinfection and healing are evaluated in vivo studies using a wound infection mouse model.

**Materials and methods**

**Chemicals and materials**

Tb$_4$O$_7$ NPs were purchased from US Research Nanomaterials, Inc. (TX, USA). 3,3,5,5-tetramethylbenzidinehydrochloride (TMB), diammonium 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS), o-phenylenediamine (OPD), and Lipid Peroxidation MDA Assay Kit were all purchased from Sigma-Aldrich (St. Louis, MO). The Live/Dead BacLight bacterial viability kit and 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) were obtained from Thermo Fisher Scientific, Inc. (MA, USA). 5-tert-butylcarbonyl-5-methyl-1-pyrroline-N-oxide (BMPO) and Cell Counting Kit-8 (CCK-8) were obtained from Dojindo Laboratories (Kumamoto, Japan). *Escherichia coli* (E. coli) and *Staphylococcus aureus* subsp. *aureus* (S. aureus) were obtained from the China General Microbiological Culture Collection Center (CGMCC, Beijing, China). Human umbilical vein endothelial cells (HUVECs) were purchased from the American Type Culture Collection (ATCC, MD, USA).

**Characterization of Tb$_4$O$_7$ NPs**

The hydrodynamic size and zeta potential of the Tb$_4$O$_7$ NPs were measured using a Zetasizer Nano-ZS (Malvern, UK). The morphology and size of the Tb$_4$O$_7$ NPs were characterized using a transmission electron microscopy (TEM, Tecnai G-20, FEI). The UV–vis absorption spectrum was recorded on a spectrophotometer (UV-3600, Shimadzu).

**Electron spin resonance spectroscopic measurements**

The electron spin resonance (ESR) measurements were carried out using a Bruker EMX ESR spectrometer according to our previous study [3, 9]. The final concentration of each component is described in each figure caption. All the ESR measurements were carried out at ambient temperature.

**Measurement of intracellular ROS**

After Tb$_4$O$_7$ NPs (100 μg/mL) treatment, bacteria (1 × 10⁹ CFU/mL) were collected by centrifugation and incubated with DCFH-DA (10 μM) for 30 min at dark, and stained bacteria were visualized with a confocal laser microscopy.

**Cytotoxicity experiments**

HUVECs were employed for investigating the cytotoxicity of Tb$_4$O$_7$ NPs. HUVECs were seeded at a density of 1 × 10⁵ cells/well in 96-well plates and incubated over night. The HUVECs were then incubated with Tb$_4$O$_7$ NPs (0–100 μg/mL) for 24 h, and cell viability was measured by MTT assay.

**Mice injury model**

BALB/c mice (8 weeks) were purchased from Pengsheng. On the day 0, the mice were anesthetized using 10% chloral hydrate. Then, the dorsal hair of mouse was shaved, full-thickness skin wounds with the diameter of 10 mm were created on the back of each mouse. After 24 h (day 1), the mice were treated with 50 μL PBS or Tb$_4$O$_7$ NPs (100 μg/mL). The Tb$_4$O$_7$ NPs were dripping on the surface of the wound.

**Hemolysis test**

Fresh blood was collected under sterile conditions from healthy BALB/c mice (n = 5) into an anticoagulation tube. The red blood cells were precipitated by centrifugation at 2000 rpm for 10 min and washed three times with PBS.
buffer solution to obtain red blood cells. The appropriate amount of red blood cells was diluted five times with PBS buffer solution to prepare a red blood cell solution. 20 μL of the diluted red blood cell suspension was mixed with a series of different concentrations of Tb4O7 NPs (0–200 μg/mL); ultrapure water was used as control. All the above samples were incubated at 37 °C for 2 h, centrifuged at 2000 rpm for 10 min, imaged, and the supernatant after centrifugation was taken in a 96-well plate to measure the absorbance at 540 nm using a microplate reader. The hemolysis rate was calculated as follows:

\[
\text{Hemolysis rate (\%)} = \left( \frac{\text{sample absorption} - \text{negative control absorption}}{\text{positive control absorption} - \text{negative control absorption}} \right) \times 100\%, \text{ and hemolysis rate exceeding 5\% is considered hemolysis.}
\]

**Results and discussion**

**Characterization of Tb4O7 NPs**

The Tb4O7 NPs used in the present study were purchased from US Research Nanomaterials, Inc. The physical characterization of Tb4O7 NPs is shown in Additional file 1: Figure S1 and included images of particle core size and shape captured by TEM, the mean and homogeneity of particle hydrodynamic size by dynamic light scattering (DLS), and particle absorption spectrum by UV–vis. According to TEM and DLS data, the dispersity of Tb4O7 NPs is poor. The mean core particle size of Tb4O7 NPs is approximately 200 nm (Additional file 1: Figure S1a, b); while the DLS result of Tb4O7 NPs is around 400 nm (Additional file 1: Figure S1c). This is mainly due to the size measured by DLS was a hydrodynamic size, and therefore the nanoparticles showed a larger hydrodynamic volume due to solvent effect in the hydrated state. The zeta potential value of Tb4O7 NPs is 31.6 mV in water. The UV–vis spectrum of Tb4O7 NPs is shown in Additional file 1: Figure S1d.

**Catalytic activity of Tb4O7 NPs as oxidase mimetics**

The oxidase-like activity of Tb4O7 NPs was evaluated using the substrate TMB. The UV–vis spectroscopy measurements show time-dependent increases in TMB oxidation catalyzed by Tb4O7 NPs, yielding a blue-colored product (Fig. 1a, b). In addition, Tb4O7 NPs can also catalyze the oxidation of ABTS and OPD (Fig. 1a). We used the oxidation of TMB as a model reaction and found that the catalytic efficiency of the Tb4O7 NPs is dependent on TMB concentrations, pH and temperature (Fig. 1c and Additional file 1: Figure S2). As shown
in Additional file 1: Figure S2a, Tb$_4$O$_7$ NPs exhibit excellent catalytic activity over a broad temperature range (25–60 °C). Moreover, an acidic condition (pH = 3.6) is conducive to the oxidase-like activity of Tb$_4$O$_7$ NPs (Additional file 1: Figure S2b). We adopted pH 3.6 and 25 °C (room temperature) as the standard conditions for subsequent studies.

Next, we determined the apparent steady-state kinetic parameters for the reaction of Tb$_4$O$_7$ NPs with TMB. Typical Michaelis–Menten curves were established (Fig. 1d). The curves were then fitted to the double-reciprocal Lineweaver–Burk plots (Fig. 1e), from which the kinetic parameters shown in Table 1 were determined.

**Effects of Tb$_4$O$_7$ NPs on the anti-oxidant defense system**

The above results show that Tb$_4$O$_7$ NPs have oxidase-like activity oxidizing TMB, ABTS, and OPD in the absence of H$_2$O$_2$. We predict that Tb$_4$O$_7$ NPs would deplete intracellular antioxidants and, eventually, disrupt the antioxidant defense systems of bacteria. To test this hypothesis, we examined the effects of Tb$_4$O$_7$ NPs on ascorbic acid (AA) oxidation in vitro. AA is an important endogenous bacterial antioxidant that prevents cellular damage from ROS. AA can be oxidized to form an intermediate ascorbyl radical (·AA), which is detectable by ESR spectroscopy [9]. As shown in Fig. 2a, the oxidation of AA was negligible within 10 min, while in the presence of Tb$_4$O$_7$ NPs the system showed a time-dependent increase in the ESR signal intensity in the first 8 min and then decreased over time. These results indicate that Tb$_4$O$_7$ NPs can accelerate AA oxidation.

In the substrate oxidation mechanism of most oxidases in nature, oxygen acts as the electron acceptor and is reduced to H$_2$O$_2$. To gain a better understanding of the oxidation of AA by Tb$_4$O$_7$ NPs, we examined whether the catalytic oxidation product of Tb$_4$O$_7$ NPs and AA produced H$_2$O$_2$. As shown in Additional file 1: Figure S3, a marked increase of H$_2$O$_2$ was detected in the presence of Tb$_4$O$_7$ compared to control (AA alone). Moreover, the production of H$_2$O$_2$ was Tb$_4$O$_7$ concentration-dependent.

Previous studies have demonstrated that several kinds of nanoparticles are capable of catalyzing the production of hydroxyl radicals by H$_2$O$_2$ [30, 31]. Therefore, we determined whether Tb$_4$O$_7$ NPs would catalyze the production of hydroxyl radicals by H$_2$O$_2$ using ESR spectroscopy. We selected BMPO as the capture agent, since BMPO can capture hydroxyl radicals to form BMPO/·OH adducts indicated by the presence of four characteristic lines on the ESR spectrum. As shown in Fig. 2b, the characteristic ESR signals of BMPO/·OH were negligible in the absence of Tb$_4$O$_7$ NPs. However, the addition of Tb$_4$O$_7$ NPs resulted in a strong ESR spectrum that displayed the four characteristic lines (1:2:2:1) of BMPO/·OH. These results clearly show that Tb$_4$O$_7$ NPs can be used as a catalyst in the decomposition of H$_2$O$_2$ to produce hydroxyl radicals.

Taken together, our results confirm that Tb$_4$O$_7$ NPs are capable of catalyzing the oxidation of biologically
relevant antioxidant agents, resulting in the production of H₂O₂. Moreover, Tb₂O₇ NPs can further catalyze the production of hydroxyl radicals via the decomposition of H₂O₂.

**Antibacterial activity of Tb₂O₇ NPs**

Both H₂O₂ and hydroxyl radicals have strong oxidizing ability and can oxidize biological macromolecules, such as proteins and phospholipids [32]. Our study found that Tb₂O₇ NPs with oxidase-like activity can catalyze the production of H₂O₂ and further produce hydroxyl radicals. Therefore, the oxidase-like activity of the Tb₂O₇ NPs makes them potentially useful as antibacterial agents. We evaluated the antibacterial activity of Tb₂O₇ NPs against *E. coli* and *S. aureus*. A colony-forming units plate counting method was used to determine the antibacterial ability (Fig. 3a, b). As compared to the PBS control group, Tb₂O₇ NPs exhibited potent antimicrobial activity against both *S. aureus* and *E. coli* in a concentration-dependent manner. At a concentration of 25 μg/mL, Tb₂O₇ NPs exhibited only modest antibacterial effects against *S. aureus*; more than 80% of the bacterial cells survived. However, when the concentration of Tb₂O₇ NPs was increased to 100 μg/mL, nearly 90% of the *S. aureus* were killed. A similar trend of antibacterial effects were observed towards the *E. coli*.

To further investigate the interaction between Tb₂O₇ NPs and bacteria, a fluorescent-based cell live/dead assay was conducted. As shown in Fig. 3c, d, Tb₂O₇ NPs exhibited significant antibacterial activity against both *S. aureus* and *E. coli*, which was consistent with the aforementioned results. The exposure of *S. aureus* cells to Tb₂O₇ NPs at a concentration of 100 μg/mL resulted in nearly 100% lethality, as evidenced by the dominant red fluorescent signal. At a concentration of 50 μg/mL, Tb₂O₇ NPs completely inhibited the bacterial growth of *E. coli*.

The morphology and membrane integrity of bacteria were then determined by SEM (Fig. 3c, d). Untreated *S. aureus* displayed a typical rod-shaped structure with a continuous, smooth surface. When exposure to the 50 μg/mL of Tb₂O₇ NPs, the *S. aureus* bacterial cell walls became partially wrinkled and discontinuance. Notably, after treatment with 100 μg/mL of Tb₂O₇ NPs, the *S. aureus* bacterial cell walls showed much more pronounced damage, indicating stronger antibacterial effects at higher concentrations of Tb₂O₇ NPs. A similar tendency was found for *E. coli*. The loss of membrane integrity of *E. coli* was observed at concentrations lower than 100 μg/mL of Tb₂O₇ NPs treatment. Moreover, Tb₂O₇ NPs were observed by SEM and SEM-energy dispersive X-ray spectroscopy (EDS) to aggregate on the surfaces of *S. aureus* and *E. coli* (Additional file 1: Figure S4).

It is known that the proton motive force decreases the local pH (as low as pH 3.0) in the cytoplasm and membrane of bacteria cells [33, 34]. Since we found that Tb₂O₇ NPs exhibit oxidase-like activity under acidic conditions, we speculate that the antibacterial mechanism of Tb₂O₇ NPs may arise from their oxidase activity to accelerate the process of bacterial cell oxidation and consumption of antioxidant biomolecules, leading to a reduction of oxygen products including H₂O₂ along with other antibacterial activity from the accumulation of ROS. To confirm this hypothesis, the intracellular levels of ROS were determined using the florescent probe, DCFH-DA (Fig. 4). For both *S. aureus* and *E. coli*, the untreated cells showed extremely weak fluorescence, indicating low levels in the formation of intracellular ROS. In contrast, bacterial cells exposed to Tb₂O₇ NPs showed high levels of ROS formed within the cellular cytoplasm, as evidenced by the strong fluorescence signal. We also found that the generation of ROS is Tb₂O₇ NPs dose-dependent (Additional file 1: Figure S5).

**In vivo wound disinfection effect of Tb₂O₇ NPs**

The above findings suggest that Tb₂O₇ NPs may have role as an antibacterial agent for bacterial infections in vivo. To assess the antibacterial capacity of Tb₂O₇ NPs in vivo, a wound infection model was constructed using BALB/c mice. A wound was introduced on the back of the mouse and an infection was established by implanting *S. aureus* into the wounded area. After infection was established, PBS or Tb₂O₇ NPs were applied to the infected wound. Figure 5a, b shows the progress of the wounds. Compared with the control (PBS treatment) group after 3 days, the wound area was reduced under Tb₂O₇ NPs treatment. After treating of 7 days with Tb₂O₇ NPs treatment, the wounds were nearly healed completely. In contrast, obvious scab was observed from the control group, indicating incomplete recovery.

**Biosafety of Tb₂O₇ NPs**

Biosafety is an important factor for antimicrobial agents designers. To assess the biosafety of Tb₂O₇ NPs, we first determined the effects of Tb₂O₇ NPs on red blood cells and HUVECs in vitro. The effect of Tb₂O₇ NPs on cell membrane disrupt was first determined by a red blood cell hemolysis assay. As shown in Fig. 6a, pure water can cause severe red blood cells hemolysis within 2 h. In contrast, the introduction of Tb₂O₇ NPs did not cause signs of hemolysis. In this experimental result, the hemolysis rate was still less than 1% at a concentration of 100 μg/mL, which fully demonstrated that Tb₂O₇ NPs have good blood compatibility. Meanwhile, the cytotoxicity tests on
mammalian cells HUVECs further confirm the biosafety of Tb$_4$O$_7$ NPs (Fig. 6b).

Then, the biosafety of Tb$_4$O$_7$ NPs in vivo were determined. As shown in Fig. 7a, the indicators in blood were within the normal range. The major mouse organs (heart, liver, spleen, lung, and kidney) were formalin-fixed and processed for the evaluation of H&E sections by

**Fig. 3** The effect of Tb$_4$O$_7$ NPs on survival rates of bacteria a CFUs of S. aureus following incubation with Tb$_4$O$_7$ NPs, b CFUs of E. coli following incubation with Tb$_4$O$_7$ NPs, c Representative fluorescence and SEM images of S. aureus after Tb$_4$O$_7$ NPs treatments. Bacterial cells were treated with 1) PBS as control, 2) 25 μg/mL Tb$_4$O$_7$ NPs, 3) 50 μg/mL Tb$_4$O$_7$ NPs or 4) 100 μg/mL Tb$_4$O$_7$ NPs. d Representative fluorescence and SEM images of E. coli after Tb$_4$O$_7$ NPs treatments. Bacterial cells were treated with 1) PBS as control, 2) 10 μg/mL Tb$_4$O$_7$ NPs, 3) 25 μg/mL Tb$_4$O$_7$ NPs or 4) 50 μg/mL Tb$_4$O$_7$ NPs. **p < 0.01 and ***p < 0.001 vs control
Fig. 4  
(a) Fluorescence images of bacterial cells. (b) Analysis of the ROS levels by microplate reader. ***p < 0.001 vs control

Fig. 5  
(a) Photographs of wounds on the backs of mice in control (PBS) and Tb$_4$O$_7$ NPs treatment groups (n = 5). Scale bar: 5 mm. (b) Related wound size in each treatment group. (c) Bacterial number of infected wounds on the 7th day. ***p < 0.001 vs control
Fig. 6  a The hemolysis ratio of red blood cells. The insert images of tubes containing red blood cells solution show the direct observation of hemolysis. Tube 1: PBS buffer; Tube 2–5: 25, 50, 100, and 200 μg/mL Tb$_4$O$_7$ NPs; Tube 6: ultrapure water.  b MTT assays determined cell viability of HUVECs after Tb$_4$O$_7$ NPs treatment.

Fig. 7  In vivo toxicity of Tb$_4$O$_7$ NPs.  a The blood biochemistry data of the mice treated with Tb$_4$O$_7$ NPs after 7 d (n = 5).  b Histological data (H&E staining images) are obtained from the major organs of mice treated with Tb$_4$O$_7$ NPs after 7 d. Scale bar = 100 μm.
histopathology (Fig. 7b). No obvious mouse organ damage was observed from Tb₄O₇ NPs treatment.

Conclusions
In summary, this study demonstrates for the first time that Tb₄O₇ NPs exhibit oxidase-like activity. In addition, the results of this study established a relationship between the oxidase-like enzyme activity of Tb₄O₇ NPs and their antibacterial properties. The data collected from this work revealed that the oxidase-like activity of Tb₄O₇ NPs was able to function with a variety of substrates, including biomolecules, and resulted in the generation of ROS, which further enhanced their antibacterial activity. The application of the antibacterial activities of Tb₄O₇ NPs were demonstrated in a wound infection mouse model. Our study provides evidence that Tb₄O₇ NPs can be utilized as an efficient antibacterial agent and the potential applications in wound healing are promising.

Additional file

Additional file 1: Figure S1. Characterization of Tb₄O₇ NPs. Figure S2. The oxidase-like catalytic activity of the Tb₄O₇ NPs. Figure S3. The concentration of H₂O₂ generated in the catalytic system. Figure S4. SEM-EDS elemental images. Figure S5. ROS levels of S. aureus.

Abbreviations
Tb₄O₇: terbium oxide; NPs: nanoparticles; H₂O₂: hydrogen peroxide; ROS: reactive oxygen species; ABTS: diammonium 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate); OPD: o-phenylenediamine; AA: ascorbic acid; DCFH-DA: 2′,7′-dichlorodihydrofluorescein diacetate; BMPO: 5-tert-butoxycarbonyl-5-methyl-1-pyrroline-3-oxide; CCK-8: Cell Counting Kit-8; E: coli; Escherichia coli; S: aureus; Staphylococcus aureus; HUVEC: human umbilical vein endothelial cells; TEM: transmission electron microscopy; ESR: electron spin resonance; CFUs: colony forming units; PI: propidium iodide; SEM: scanning electron microscope; DLS: dynamic light scattering; EDS: energy dispersive X-ray spectroscopy.

Authors’ contributions
CL, YS, and XL prepared and performed the experiments. YS, XL and YL analyzed the data and interpreted the results. XT, SF and YP conceived and designed the study. CL, YS, and XL prepared and performed the experiments. YS, XL and YL analyzed the data and interpreted the results. XT, SF and YP conceived and supervised the study. The manuscript was written by XT and XJ and revised critically by JY and MB. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
All data generated or analyzed during this study are included in this published article and its additional file.

Consent for publication
All authors agree to be published.

Ethics approval and consent to participate
The protocols and the use of animals were approved by and in accordance with the animal welfare committee of Soochow University.

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References
1. Fischbach MA, Walsh CT. Antibiotics for emerging pathogens. Science. 2009;325:1089–93.
2. Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. Nat Rev Microbiol. 2010;8:423–35.
3. Tian X, Jiang X, Welch C, Copley TR, Wong TY, Chen C, Fan S, Chong Y, Li R, Ge C, Chen C, Yin JJ. Bactericidal effects of silver nanoparticles on lactobacilli and the underlying mechanism. ACS Appl Mater Interfaces. 2018;10:8443–50.
4. Mahmoudi M, Serpooshan V. Silver-coated engineered magnetic nanoparticles are promising for the success in the fight against antibacterial resistance threat. ACS Nano. 2012;6:2656–64.
5. Panacek A, Kvitěk L, Smekalova M, Veceraova R, Kolar M, Roderova M, Dycka F, Sebelka M, Pucek R, Tomanec G, Zbooril R. Bacterial resistance to silver nanoparticles and how to overcome it. Nat Nanotechnol. 2018;13:1506–20.
6. Jiang B, Duan D, Gao L, Zhou M, Fan K, Tang Y, Xi J, Bi Y, Tong Z, Gao GF, Xie N, Tang A, Nie G, Liang M, Yan X. Standardized assays for determining the catalytic activity and kinetics of peroxidase-like nanoparticles. Nat Protoc. 2018;13:65–71.
7. Gao L, Fan K, Yan X. Iron oxide nanzyme: a multifunctional enzyme mimic for biomedical applications. Theranostics. 2017;7:3207–27.
8. Wang X, Hu Y, Wei H. Nanzymes in bionanotechnology: from sensing to therapeutics and beyond. Inorg Chem Front. 2016;3:41–60.
9. Chen C, Fan SH, Li C, Chong Y, Tian X, Zheng JW, Fu PP, Jiang XM, Warner WG, Yin JJ. Platinum nanoparticles inhibit antioxidant effects of vitamin C via ascorbate oxidase-mimetic activity. J Mater Chem B. 2016;4:7895–901.
10. Luo W, Zhu C, Su S, Li D, He Y, Huang Q, Fan C. Self-catalyzed self-limiting growth of glucose oxidase-mimicking gold nanoparticles. ACS Nano. 2010;4:7451–8.
11. Xia X, Zhang J, Lu N, Kim M, Ghal K, Xu W, McKenzie E, Liu J, Ye H. Pd–Ir core-shell nanocubes: a type of highly efficient and versatile peroxidase mimic. ACS Nano. 2015;9:9994–10004.
12. Yao J, Cheng Y, Zhou M, Zhao S, Lin S, Wang X, Wu J, Li S, Wei H. ROS scavenging MnO₂ nanoymes for in vivo anti-inflammation. Chem Sci. 2018;9:2927–33.
13. Ghosh S, Roy P, Karmodak N, Jemmis ED, Mugesh G. Nanoisozymes: crystal-facet-dependent enzyme-mimetic activity of V_{2}O_{5} nanomaterials. Angew Chem Int Ed Engl. 2018;57:45–10.

14. Singh N, Savanur MA, Srivastava S, D'Silva P, Mugesh GA. Redox modulatory Mn_{2}O_{3} nanoenzyme with multi-enzyme activity provides efficient cytotoxicity to human cells in a Parkinson's disease model. Angew Chem Int Ed Engl. 2017;56:14267–71.

15. Lin L, Song X, Chen Y, Rong M, Zhao T, Wang Y, Jiang Y, Chen X. Intrinsic peroxidase-like catalytic activity of nitrogen-doped graphene quantum dots and their application in the colorimetric detection of H_{2}O_{2} and glucose. Anal Chim Acta. 2015;869:89–96.

16. Zheng AX, Cong ZX, Wang JR, Li J, Yang HH, Chen GN. Highly-efficient peroxidase-like catalytic activity of graphene dots for biosensing. Biosens Bioelectron. 2013;49:19–24.

17. Wang H, Liu C, Liu Z, Ren J, Qu X. Specific oxygenated groups enriched graphene quantum dots as highly efficient enzyme mimics. Small. 2018;14:e1703710.

18. Hassanzadeh J, Khataee A. Ultrasensitive chemiluminescent biosensor for the detection of cholesterol based on synergistic peroxidase-like activity of MoS_{2} and graphene quantum dots. Talanta. 2018;178:992–1000.

19. Wang Z, Dong K, Liu Z, Zhang Y, Chen Z, Sun H, Ren J, Qu X. Activation of biologically relevant levels of reactive oxygen species by Au/g-C_{3}N_{4} hybrid nanozyme for bacteria killing and wound disinfection. Biomaterials. 2017;113:145–57.

20. Cai S, Jia X, Han Q, Yan X, Yang R, Wang C. Porous Pt/Ag nanoparticles with excellent multifunctional enzyme mimic activities and antibacterial effects. Nano Res. 2017;10:2056–69.

21. Tao Y, Ju E, Ren J, Qu X. Bifunctional mesoporous silica-supported gold nanoparticles: intrinsic oxidase and peroxidase catalytic activities for antibacterial applications. Adv Mater. 2015;27:1097–104.

22. Chen Z, Wang Z, Ren J, Qu X. Enzyme mimicry for combating bacteria and biofilms. Acc Chem Res. 2018;51:789–99.

23. Chen S, Quan Y, Yu YL, Wang JH. Graphene quantum dot/silver nanoparticle hybrids with oxidase activities for antibacterial application. ACS Biomater Sci Eng. 2017;3:313–21.

24. Ge C, Wu R, Chong Y, Fang G, Jiang X, Pan Y, Chen C, Yin JJ. Synthesis of Pt hollow nanodendrites with enhanced peroxidase-like activity against bacterial infections: implication for wound healing. Adv Funct Mater. 2018;28:1801484.

25. Fang G, Li W, Shen X, Perez-Aguilar JM, Chong Y, Gao X, Chai Z, Chen C, Ge C, Zhou R. Differential Pd-nanocrystal facets demonstrate distinct antibacterial activity against Gram-positive and Gram-negative bacteria. Nat Commun. 2018;9:129.

26. Loo AE, Wong YT, Ho R, Wasser M, Du T, Ng WT, Halliwell B. Effects of hydrogen peroxide on wound healing in mice in relation to oxidative damage. PLoS ONE. 2012;7:e49215.

27. Nahm CW. Varistor characteristics of ZnO/NiO/MnO2/Nb2O5 semiconducting ceramics with Tb2O3 addition. J Mater Sci Mater El. 2015;26:4144–51.

28. Gao H, Zhou Y, Chen KQ, Li XL. Synthesis of Tb2O3 complexes with reduced graphene oxide for Rhodamine-B absorption. Mater Res Bull. 2016;77:111–4.

29. Castillo-Garcia ML, Aguilar-Caballos MP, Gomez-Hens A. Application of Tb(4)O(7) nanoparticles for lasalocid and salicylate determination in food analysis. J Agric Food Chem. 2012;60:11741–7.

30. Tian X, Sun Y, Fan S, Boudreau M, Chen C, Ge C, Yin JJ. Photogenerated charge carriers in molybdenum disulfide quantum dots with enhanced antibacterial activity. ACS Appl Mater Interfaces. 2019;11:4858–66.

31. Tao W, Zhang H, Chong Y, Warner WC, Yin JJ, Wu XC. Probing hydroxyl radical generation from H_{2}O_{2} upon plasmon excitation of gold nanorods using electron spin resonance: molecular oxygen-mediated activation. Nano Res. 2016;9:1663–73.

32. Sun HJ, Gao N, Dong K, Ren JS, Qu XG. Graphene quantum dots-bandaids used for wound disinfection. ACS Nano. 2014;8:6202–10.

33. Koch AL. The pH in the neighborhood of membranes generating a protonmotive force. J Theor Biol. 1986;120:73–84.

34. Xiu ZM, Zhang QB, Puppala HL, Colvin VL, Alvarez PJ. Negligible particle-specific antibacterial activity of silver nanoparticles. Nano Lett. 2012;12:4271–5.