REVIEW

Multienzymes activity of metals and metal oxide nanomaterials: applications from biotechnology to medicine and environmental engineering

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Abstract
With the rapid advancement and progress of nanotechnology, nanomaterials with enzyme-like catalytic activity have fascinated the remarkable attention of researchers, due to their low cost, high operational stability, adjustable catalytic activity, and ease of recycling and reuse. Nanozymes can catalyze the same reactions as performed by enzymes in nature. In contrast the intrinsic shortcomings of natural enzymes such as high manufacturing cost, low operational stability, production complexity, harsh catalytic conditions and difficulties of recycling, did not limit their wide applications. The broad interest in enzymatic nanomaterial relies on their outstanding properties such as stability, high activity, and rigidity to harsh environments, long-term storage and easy preparation, which make them a convenient substitute instead of the native enzyme. These abilities make the nanozymes suitable for multiple applications in sensing and imaging, tissue engineering, environmental protection, satisfactory tumor diagnostic and therapeutic, because of distinguished properties compared with other artificial enzymes such as high biocompatibility, low toxicity, size dependent catalytic activities, large surface area for further bioconjugation or modification and also smart response to external stimuli. This review summarizes and highlights latest progress in applications of metal and metal oxide nanomaterials with enzyme/multienzyme mimicking activities. We cover the applications of sensing, cancer therapy, water treatment and anti-bacterial efficacy. We also put forward the current challenges and prospects in this research area, hoping to extension of this emerging field. In addition to therapeutic potential of nanozymes for disease prevention, their practical effects in diagnostics, to monitor the presence of SARS-CoV-2 and related biomarkers for future pandemics will be predicted.

Keywords: Nanozyme, Metal, Metal oxide, Sensing and biosensing, Cancer, Therapeutic, Diagnostics

Introduction
Enzymes, as biological macromolecules, are mainly composed of proteins, which can efficiently and selectively catalyze a diverse biochemical reactions [1, 2]. They play a notable function in various fields, such as energy production processes, biosensing, the food industry, and biofuels [3–6]. However, they have some drawbacks, such as product complexity, harsh catalytic conditions and low operational stability because of digestion and denaturation. In addition, it has high costs in preparation and purification [7, 8]. To address these issues, nanomaterial with enzyme-like characteristics (nanozyme) was applied as a novel alternative candidate. Artificial enzymes have attracted the significant attention of researchers due to their higher stability, low cost, flexibility and tunable catalytic activities [9–11]. Compared with other artificial enzymes, nanozymes possess outstanding properties...
such as their size and structure dependent catalytic activities, multi enzyme activity, large surface area, smart response and self-assembly capability [12, 13]. On the basis of these outstanding properties, nanozymes have been widely utilized for disease diagnosis and treatment, chemical sensing, environmental protection and antibacterial agents [7, 14–17]. Up to now, lots of nanomaterials have been uncovered to mimic several natural enzymes, such as peroxidase, oxidase, catalase, superoxide dismutase (SOD), phosphatase, nuclease, esterase, protease and ferroxidase [18]. Since the finding of Fe3O4 nanoparticles as peroxidase mimics in 2007 [19], a large amount of studies on metal and metal oxide nanomaterials have been reported. For example, Au, Pt, Pd, Co3O4, CeO2, CuO, MnO2, NiO, V2O5 nanocomposites have been shown to possess a unique enzyme-like property [20–28]. Metal and metal oxide nanomaterial played great role in progress and development of enzyme mimic technology, due to their unique combination of redox chemistry, optical and electrical properties [29–32]. Interestingly, some nanomaterial can mimic the function of two or three enzymes. It has been reported that the simultaneous expression of multiple enzymes is more effective than single expression to remove harmful reactive oxygen species [33]. When designing a cascade reaction, it is often appropriate to use multiple nanozyme as the cascade catalyst. In this review, we present a comprehensive review of applications of metal and metal oxide nanomaterial in terms of chemical sensing and biosensing, cancer treatment, water purification and anti-bacterial efficiency (Table 1). We also highlight some recent examples of multi-enzyme applications in catalysis. Because of the space limit, we could not cover all the related publications. However, we summarize recent research works on metal and metal oxide based nanzyme in Table 1. In the last section, the current challenges and future opportunities of metal and metal oxide-based nanomaterials are also discussed. We hope that the present review will be of great benefit for development of novel nanomaterials in the fields of medicine, chemistry, biology and nanotechnology.

**Nanozymes for sensing application**

Metal and metal oxide-based nanomaterials with substantial properties have been widely applied for several analytical purposes. The principle detection is divided into two categories: (1) the target activates or deactivates a reaction between the nanzyme and the agent, (2) the presence of the nanzyme and its reaction with the agent indirectly indicates the amount of target. According to previous reports, the application of such nanomaterial includes detection of a variety of important targets, such as tumor markers, small biomolecules and metal ions [18, 28, 34].

**Tumor markers**

Synthesize nanomaterials within cage-like protein templates has been demonstrated to be a suitable approach to produce uniform [35]. Ferritin nanocages provide surface modification and specific targeting abilities for synthesizing ferritin-based nanozymes [36]. Biomineralization synthesis of cobalt nanzyme in SP94-ferritin nanocage was reported for prognostic diagnosis of hepatocellular carcinoma (HCC) [37]. In this report, ferritin-based cobalt nanzyme (HccFn(Co3O4)) was designed for HCC diagnosis and therapy. SP94 peptide was modified onto the exterior surface of ferritin nanocage (HccFn) for specifically binding to HCC cells. HccFn(Co3O4) nanozymes specifically bound to HCC tissues and catalyze the oxidation of peroxidase substrate diaminobenzidine (DAB) to produce deep brown colorimetric reaction. In comparison with Fn(Co3O4) control group, HccFn(Co3O4) nanozymes specifically recognized and visualized HCC tissues and could distinguish tumor cells from normal tissues (Fig. 1).

The nanomaterial-mediated colorimetric sensor is an attractive system for advance instrument-free bioanalysis due to its unique advantages of simplicity in operating analysis via camera or smartphone [38, 39]. Several colorimetric assays based on the 3,3,5,5-tetramethylbenzidine (TMB)-H2O2 system catalyzed by enzyme mimic nanomaterials have been extensively developed for immunoassay [40–42]. For instance, Alizadeh et al. present a paper-based microfluidic colorimetric immunosensor for the detection of carcinoembryonic antigen (CEA), using Co3(OH)2CO3-CeO2 nanocomposite with extraordinary intrinsic peroxidase like activity [43]. The proposed immunosensor facilely prepared by modifying mixture of ionic liquid and chitosan functionalized primary antibodies (Ab1) on the surface of paper. Co3(OH)2CO3-CeO2 peroxidase mimicking enzyme was functionalized secondary antibodies (Ab2) and used as a signal tag. Co3(OH)2CO3-CeO2 nanocomposite catalyzed the oxidation of 3,3′,5,5′-tetramethyl benzidine in the presence of H2O2, resulting in a color change, which acquired as the immunosensor response. The color change was distinct by the naked eye and analyzed by an installed application on the smartphone (Fig. 2).

In colorimetric assays, color changes and photothermal effect of TMB-H2O2 colorimetric system have been prospected [44]. In this regard, nanoparticle (NPs)-mediated photothermal immunoassay platform was developed for detection of prostate-specific antigen (PSA) using a common thermometer as the quantitative signal reader [45]. The iron oxide NPs-labeled antibody was applied as the detection probe, on basis of sandwich-type proof-of-concept immunoassay. In the immunoassay, iron oxide artificial enzyme demonstrated color changes and also a
strong NIR laser-driven photothermal effect, simultaneously. The oxidized TMB acted as a highly sensitive photothermal probe to convert the immunoassay signal into heat via its photothermal effect (Fig. 3).

Aptamers are artificial synthetic single-stranded DNA or RNA oligonucleotides, which can bind with various targets such as protein, peptide, organic/inorganic molecule, and cell with high affinity and specificity. Aptamer with superiority to antibodies, including high stability, ease of synthesis, low cost and easy chemical modification, have attracted a lot of attention in biomedical and bioanalysis research [46–48]. Zhao et al. selected three hairpin anti-MUC1 DNA aptamers for construction of a sensitive electrochemical aptasensor based on

| Enzyme                  | Nanomaterial                  | Application | References |
|-------------------------|-------------------------------|-------------|------------|
| Peroxidase              | HccFn(Co₃O₂₇)                 | Sensing     | [37]       |
| Peroxidase              | Co₉(OH)₂CO₃-CeO₂              | Sensing     | [43]       |
| Peroxidase              | Iron oxide                    | Sensing     | [45]       |
| Peroxidase              | PtPd                          | Sensing     | [49]       |
| Oxidase                 | Ag-CoFe₂O₄/rGO               | Sensing     | [55]       |
| Peroxidase              | CuO/Pt                        | Sensing     | [56]       |
| Peroxidase              | (rGO)-PdAu                    | Sensing     | [60]       |
| Peroxidase              | Au                            | Sensing     | [61]       |
| GSH-oxidase and peroxidase | CuO                           | Sensing     | [65]       |
| Peroxidase              | Au@Pt                         | Sensing     | [70]       |
| Peroxidase              | GO–AuNP                       | Sensing     | [71]       |
| Peroxidase              | Cu₂O/rGO                     | Sensing     | [74]       |
| Oxidase                 | CoO₂H                        | Sensing     | [77]       |
| Peroxidase              | FeMnO₃                       | Sensing     | [80]       |
| Peroxidase              | CuFe₂O₃/Cu₃S₄/Ppy            | Sensing     | [81]       |
| Peroxidase              | CuO                          | Sensing     | [85]       |
| Peroxidase              | Fe₃O₄ NPs/rGO/MoS₂            | Sensing     | [86]       |
| Peroxidase              | CuO/VO₂-rGO                  | Sensing     | [91]       |
| Peroxidase              | Pt-Pd                         | Sensing     | [97]       |
| GSH-oxidase and peroxidase | MnO₂                         | Therapeutics | [110]     |
| Peroxidase              | FeCePW                       | Therapeutics | [114]     |
| Peroxidase              | Copper peroxide              | Therapeutics | [116]     |
| Peroxidase              | SnFe₂O₄                      | Therapeutics | [118]     |
| Peroxidase              | Fe₃O₄@MSN                    | Therapeutics | [122]     |
| Catalase                | MnFe₂O₄                      | Therapeutics | [130]     |
| Catalase                | MnO₂                         | Therapeutics | [132, 133] |
| Catalase                | Pt                            | Therapeutics | [134]     |
| Catalase and oxidase    | MoO₃–x                       | Therapeutics | [136]     |
| Peroxidase and oxidase  | Au@HCNs                      | Therapeutics | [144]     |
| Catalase and superoxide dismutase | NCeO₂-PEI-MoS₂   | Therapeutics | [145]     |
| Catalase                | Pt-CuS                       | Therapeutics | [151]     |
| Peroxidase and oxidase  | GQD/AgNP                     | Antibacterial | [159] |
| Oxidase, peroxidase and catalase | Pt/Ag        | Antibacterial | [160]     |
| Oxidase and peroxidase  | MSN-Au                       | Antibacterial | [164]     |
| Peroxidase              | CuO                          | Antibacterial | [167]     |
| Oxidase and peroxidase  | Pd                            | Antibacterial | [170]     |
| Peroxidase              | Fe₂O₃                        | Water purification | [182, 185, 188] |
| Peroxidase              | Fe₃O₄                        | Water purification | [183]     |
| Peroxidase              | CuFe₂O₄                      | Water purification | [184]     |
| Peroxidase              | FeₓNbₓOₙ₋ₙ₋ₙ₋ₙ                 | Water purification | [187]     |
catalytic hairpin assembly coupled with PtPdNPs peroxidase-like activity [49]. After binding with target protein, Apt-HP1 containing aptamer sequence was opened and MUC1-aptamer binding complex formed (Fig. 4). Next, the exposed segment of HP1 would attack HP2 immobilized on the electrode to form a double strand structure. Then, the new exposed segment of HP2 hybridized with the toehold of PtPdNPs modified HP3. Finally, MUC1-A was released via the strand displacement process, and the released MUC1-A could participate in the subsequent reaction cycles. The carried PtPdNPs, as a mimic peroxidase probe, catalyzed the TMB by H$_2$O$_2$, leading to the electrochemical signal generation.

**Metal ions**

Most studies on metal ions sensing with nanozymes have been devoted to mercury ions (Hg$^{2+}$) [9, 50, 51]. Mercury is a toxic metal ion that in the environment can produce several harmful effects on people’s health like brain, heart, kidneys and central nervous system damages [52, 53]. Through the bacteria action in a lake and ocean, Hg$^{2+}$ converts into more toxic organic mercury and accumulates in aquatic organisms [54]. Thereupon, it can accumulate continuously in the body through water and food. In a report, dual colorimetric and SERS detection of Hg$^{2+}$ was developed based on the stimulus of intrinsic oxidase-like catalytic activity of Ag-CoFe$_2$O$_4$/rGO nanocomposites [55]. CoFe$_2$O$_4$ nanoparticles in Ag-CoFe$_2$O$_4$/rGO nanocomposites exhibited an oxidase-like activity, which can quickly catalyze the oxidation of typical chromogenic substrates 3,3',5,5'-tetramethylbenzidine (TMB) in the presence of dissolved oxygen. The introduction of Hg$^{2+}$ led to enhancement in oxidase-like activity of the Ag-CoFe$_2$O$_4$/rGO nanocomposites due to the formation of the Ag-Hg alloy. Owing to the existence of the Ag nanoparticles the prepared nanocomposites have also been demonstrated to be efficient SERS substrate. In another report, colorimetric detection of Hg$^{2+}$ in various groundwater samples was successfully performed using CuO/Pt Nanoflowers (NFs). In the presence of Hg$^{2+}$, the peroxidase activity of CuO/Pt NFs was hindered, because the formation of the CuO/Pt-Hg trimetallic amalgam [56].
Lead (Pb²⁺) is known as a non-biodegradable, toxic and perdurable metal ion. It has a strong negative effect on children's behavior and serious damage to the brain, immune system of many life tissues including liver, brain, kidney and also immune and central nervous system [57–59]. Xu et al. reported colorimetric and electrochemiluminescence dual mode sensing of lead ion biomolecules using graphene oxide (rGO)-PdAu probe [60]. Pb²⁺-specific DNAzyme was immobilized onto rGO-PdAu-glucose oxidase (GOx). The thiol modified Pb²⁺-dependent DNAzyme was self-assembled onto the surface of the flower-like Au NPs modified ECL detection zone to hybridize with rGO-PdAu-GOx labeled oligonucleotide. Upon introducing of Pb²⁺ into the prepared system, the double helix structure of DNA was cleaved, resulting in the release of rGO-PdAu-GOx probe to catalyze the oxidation and color change of TMB. Meanwhile, the concentration of H₂O₂ is proportional to the luminol ECL system, which constitutes a new mechanism for ECL detection of Pb²⁺ (Fig. 5).

Inspired by the aggregation-induced emission (AIE) properties, the catalytic activity of metal nanozyme could be altered upon aggregation, because both optical and catalytic properties of metal nanocomposites are highly dependent on their size and morphology. It was found that the Pb²⁺-induced aggregation can greatly accelerate the peroxidase-like activity of Au nanoclusters (Au-NCs) [61]. In the absence of Pb²⁺, Au-NCs could catalyze the TMB oxidation by H₂O₂ in a relatively slow reaction rate. After the Pb²⁺-induced aggregation, the peroxidase activities of Au-NCs toward oxidation of TMB substrate in the presence of H₂O₂ are nearly tenfold increased.

Some cascade reactions were configured between enzyme-like nanomaterials and natural enzymes [62, 63]. This cascade catalytic system must be carried out in two steps, because the optimal pH conditions for each enzyme is different. To address the limitation of different conditions, a single nanomaterial with dual activity has been constructed to mimic enzyme cascade reaction [64]. He et al. described a self-cascade system based on cupric oxide nanoparticles as dual-functional enzyme mimics for ultrasensitive detection of silver ions [65]. Cupric oxide nanoparticles (CuO NPs), as the dual-functional nanozyme, demonstrated the intrinsic GSH-oxidase and peroxidase-like activity coupling with terephthalic acid (TA) and GSH to construct a self-cascade fluorescent system. CuO NPs effectively catalyze the oxidation of GSH by oxygen to produce glutathiol (GSSG) and hydrogen peroxide, following to catalyze the decomposition of hydrogen peroxide into hydroxyl. Then, a highly fluorescent product TAOH was formed by oxidation of terephthalic acid (TA) in the presence of hydroxyl radical. Thus,
in the presence of GSH, the turn-on fluorescence signal of oxidation hydroxyterephthalate (TAOH) is created. Introduction of the Ag$^{+}$ ions cause to inhibition of the fluorescence of H$_2$O$_2$-TA-CuO NPs reaction system. It is due to that Ag$^{+}$ ions can react with the H$_2$O$_2$ intermediate product resulted from the oxidation of GSH.

Until now, many assays for single heavy metal ions have been reported [66–68]. However, some efforts have been made to develop simultaneous detection of metal ions. Hg$^{2+}$ and Ag$^{+}$ are usually coexisting in water, soil and even biological systems [69]. Peng et al. prepared core–shell Au@Pt nanoparticles for simultaneous colorimetric detection of Hg$^{2+}$ and Ag$^{+}$ [70]. Both Hg$^{2+}$ and Ag$^{+}$ were found to intensively inhibit the catalytic activity of Au@Pt NPs. The complexation of sodium dodecyl sulfate (SDS) shields interference metal ions such as Mn$^{2+}$, Sr$^{2+}$, Zn$^{2+}$, Fe$^{3+}$, Co$^{2+}$, Cu$^{2+}$ and Bi$^{3+}$, to obtain specific respond of Hg$^{2+}$ and Ag$^{+}$. As well as, L-cysteine can be used to mask Hg$^{2+}$ in the presence of Ag$^{+}$. In another study, Colorimetric detection of Hg$^{2+}$ and Pb$^{2+}$ was achieved based on peroxidase-like activity of graphene oxide–gold (GO–AuNP) nanohybrids [71]. Single-stranded DNA (ssDNA) were stable against the salt-induced aggregation of GO–AuNP nanohybrids, whereas double stranded DNA (dsDNA) did not hinder salt-induced GO–AuNP nanohybrids aggregation. On the basis of the ability of GO–AuNP nanohybrids to differentiate between ssDNA and dsDNA, label-free colorimetric method for the detection of Hg$^{2+}$ and Pb$^{2+}$ was developed. With addition of Hg$^{2+}$ or Pb$^{2+}$, ssDNA formed a hairpin-like or a quadruplex structure, and these conformational changes led to the salt-induced aggregation of GO AuNP nanohybrids. After addition of TMB and H$_2$O$_2$, the colorimetric signal was significantly decreased compared to that in the absence of Hg$^{2+}$ or Pb$^{2+}$.

**Biomolecules**

Glucose is the main energy source for cellular metabolism and function of human bodies. However, people with glucose excessive suffer from diabetes mellitus.
Diabetes can cause serious health problems, such as strokes, heart attacks, high blood pressure, and even blindness or death [72, 73]. Guo and co-workers fabricated Ag-Cu₂O/reduced graphene oxide nanocomposites with peroxidase-like catalytic reaction for (Surface-enhanced Raman spectroscopy) SERS detection of glucose [74]. SERS facilitate highly sensitive and selective identification of analytes such as glucose. Ag-Cu₂O/rGO nanocomposites operate as both peroxidase nanozyme and SERS substrates; they speed up the reaction between TMB and H₂O₂. A SERS method has been designed based on the ability of glucose oxidase (GOx) to catalyze the oxidation of glucose to gluconolactone and H₂O₂. In this method, glucose was determined by the catalytic oxidation of TMB in the presence of GOx and glucose. Discern between diabetic and normal individuals by determining the glucose levels within a fingerprint is the most important feature of this work (Fig. 6).

Ascorbic acid (AA) neurochemicals, used as an enzyme cofactor and antioxidant. Meanwhile, AA plays a critical role of anti-oxygenation and resists the cells damage from free radicals. High level of AA can selectively kill colorectal cancer cells as a pro-oxidant anticancer agent [75, 76]. Therefore, methods for simple, fast, and effective AA assay suitable for the biological systems are required. Ding et al. the CoOOH-TMB oxidative system for colorimetric and test strip based detection of ascorbic acid [77]. CoOOH nanoflakes directly oxidize TMB (colorless) to blue oxTMB with a characteristic absorption peak at 652 nm. In the presence of ascorbic acid (AA), the absorbance decreased because AA reduces oxTMB. Furthermore, the CoOOH-TMB systems can be further developed into a paper-strip-based assay for determination of AA in rat brain (Fig. 7).

By reacting with H₂O₂, some small bioactive molecules like dopamine and glutathione (GSH) have
been determined based on their inhibition effects on peroxidase enzyme mimics [78, 79]. For example, GSH in human serum samples was determined using FeMnO₃ nanoparticles-filled polypyrrole nanotubes as peroxidase mimic [80]. More, with Yang’s sensing strategy, selective colorimetric detection of dopamine was successfully executed in real samples [81].

### Cancer cell and bacteria

Cancer is one of the fatal sicknesses and has become a major public worry in the world [82]. Presently, early diagnosis has been made to be the most effective way to raise survival rate [83]. Thus, it is highly needed to develop sensitive, rapid and specific methods to detect and quantification of cancer cells at early stage [84]. The conjuration of aptamer or a ligand with nanozymes can be employed for cancer cells detection. For instance, MCF-7 circulating tumor cells were detected by an electrochemical cytosensor with effective surface recognition between specific mucin 1 protein (MUC-1) over-expressed on the MCF-7 cell membranes and MUC-1 aptamer [85]. The CuO nanozyme was used as a signal-amplifying nanoprobes with reduced graphene oxide/gold nanoparticles composites (rGO/AuNPs composites) as a support material (Fig. 8I). The fabricated “sandwich” structure can help to reach on the acceptable sensitivity of the proposed cytosensor.

The immunomagnetic sensor was also developed for electrochemical detection of MCF-7 circulating tumor cells [86]. Fe₃O₄ NPs magnetic beads act as both separation and enrichment CTCs and as enzyme mimics with rGO/MoS₂ synergistic catalysis (Fig. 8II). The CTCs could be separated and enriched on the magnetic glassy carbon electrode (MGCE) by Fe₃O₄ NPs coated aptamer. Electrochemical current of TMB redox product was generated via Fe₃O₄ NPs/rGO/MoS₂ catalytic ability.

Recently, several studies reported that folate-modified nanozymes could detect cancer cells with over-expressed folate receptor [87–90]. In Alizadeh and co-workers’ study, the novel method was developed for electrochemical cancer cell detection using CuO/WO₃ nanoparticle decorated graphene oxide nanosheet (CuO/WO₃-GO) conjugated with folic acid (FA) [91]. In the absence of cancer cells, o-Phenylenediamine (OPD) oxidized on the Au electrode in the presence of H₂O₂, while FA/CuO/WO₃-GO with peroxidase like activity reacted with folate receptor of cancer cells seeded on 96-well plate, catalyzed the oxidation of OPD in presence of H₂O₂ (Fig. 9). Actually, in the presence of cancer cells, the response signal decreased, because some amount of H₂O₂–OPD system participated in chemical reaction and removed from the electrode. In this way, cancer cells detected in wide linear range and a low detection limit.

Infectious diseases induced by bacteria considered a cause of more than 25% of all global deaths [92]. Pathogen detection is an important step in the inhibition of these types of infectious and deadly diseases [93]. Several studies have been employed for bacteria detection using nanozymes as probing elements [94–96]. Recently, Cheng et al. reported nanozyme mediated dual-immunoassay integrated with smartphone for use in simultaneous
They applied platinum-palladium (Pt–Pd) nanoparticles as a signal amplifier in a dual-lateral flow immunoassays (LFIA) and for simultaneous colorimetric detection of Salmonella Enteritidis and E. coli O157:H7. Smartphone-based device and its ability to image provide a portable and cost-effective platform for tracking bacterial contamination along the entire food chain.

**Nanozymes for therapeutics application**

Reactive oxygen species (ROS), is a general expression that describes the chemical species generated upon incomplete reduction of oxygen [98]. ROS including hydrogen peroxide, superoxide anion, hydroxyl radical and singlet oxygen have the potential to kill cancer cells by destroying biomolecules such as DNA, proteins and lipids [99]. In recent years, substantial achievements have been made in ROS-based nanomedicine, especially in cancer and bacterial infection [100–102]. The development of nanotechnology has favored the production of several ROS-generation materials with enzyme-mimic characteristics [103]. Metal and metal oxide nanozymes with peroxidase- and catalase-like activities, can convert endogenous biological H₂O₂ into highly cytotoxic OH· and O₂·− species [104]. Furthermore, developing nanotechnology and nanozymes with special ROS-regulating properties solve the problem of the instability of ROS-based therapeutics. In this section, nanozymes catalytic mediated cancer therapies are discussed, which cover (photodynamic therapy) PDT, chemodynamic therapy (CDT), sonodynamic therapy (SDT) and photothermal therapy (PTT). Furthermore, the Metal and metal oxide-based nanozymes for antimicrobial therapies are summarized.

**Chemodynamic therapy (CDT)**

Chemodynamic therapy (CDT) is an emerging cancer treatment strategy that damage tumor cells with a localized Fenton reaction. In CDT process iron mediated Fenton reaction induces intracellular oxidative stress by converting less reactive H₂O₂ into OH·, one of the most detrimental ROS [105, 106]. Up to now, iron oxide and other metal oxide nanocomposite enzyme mimic are capable of decomposing H₂O₂ into OH· through Fenton-like reactions [107]. Researchers have been widely studied CDT treatment method because of its high tumor specificity, lower side effects and minimal invasiveness. Generally, transition metal ions (e.g., Fe, Co, Ni, Cu, and Mn) used as the CDT agents to catalyze the decomposition of hydrogen peroxide (H₂O₂) and produce high-toxicity hydroxyl radicals (·OH) (Typical reaction: Fe²⁺ + H₂O₂ → Fe³⁺ + ·OH + OH⁻). Biomolecular substances including nucleic acids, lipids and proteins in tumor cells are destroyed as a result of oxidative stress [108, 109]. Conceivably, some challenges like overexpressed glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH) in tumor cells, low H₂O₂ concentration and requirement of strong acidic chemical environment obstacles CDT. Lin et al. reported enhanced chemodynamic therapy based on MnO₂ nanoagent with Fenton-like Mn²⁺ delivery and GSH depletion properties [110]. The MnO₂ was established on the surface of thiol-functionalized mesoporous silica (MS) NPs, leading to the formation of MnO₂-coated MS NPs (MS@MnO₂ NPs). Upon uptake of the MS@MnO₂ NPs by cancer cells, the MnO₂ layer would simultaneously release Mn²⁺ with superior Fenton-like activity to transform endogenous H₂O₂ produced into the highly toxic OH· and deplete intracellular GSH to inhibit OH· scavenging (Fig. 10a, b). As well as, the potential of MnO₂ shell as a
gatekeeper for controlled drug release showed by loading hydrophobic anticancer drug camptothecin (CPT) into the PEGylated MS@MnO₂ NPs. Hematoxylin and eosin (H&E)-stained images demonstrated that tumor tissues treated with MS@MnO₂-CPT suffered more intense damage than other control group, which indicates enhanced chemodynamic efficacy of MS@MnO₂-CPT for theranostic applications (Fig. 10c).

Until now, almost all developed CDT agents are acidity dependent (optimum Fenton reaction pH: 2–4) and a few studies have been carried out to develop wide pH range-responsive CDT agents [111]. However, the neutral-pH

Fig. 8 Schematic representation of the cytosensor for detection of MCF-7 using (I) CuO and (II) Fe₃O₄ nanozyme
conditions at the solid tumor surface resulting from abundant vessel distribution and sufficient oxygen supply undo the effect of acidity-activated nanoagents and even induce tumor recurrence and metastasis after treatment [112, 113]. Zhao’s group synthesized Ferrous-cysteine–phosphotungstate nanoagent for enhanced cancer chemodynamic therapy that breaks through the limitation of a neutral pH [114]. The advantages from the addition of phosphotungstate and cysteine to formation of a Fe\(^{3+}\) chelating complex inhibited the formation of inert Fe(OH)\(_x\), and accelerate electron transfer between ferric and ferrous ions, respectively (Fig. 11a).

To investigate the OH\(^{·}\) generation ability of the ferrous-cysteine–phosphotungstate nanoparticles (FcPWNPs), electron spin resonance (ESR) spectroscopy is conducted. As can be seen in Fig. 11b, FcPWNPs show representative hydroxyl radicals with pH-dependent tendency. The strong cytotoxicity against cancer cells with an H\(_2\)O\(_2\) dose-dependent tendency was achieved inspired by the high OH\(^{-}\) production performance across a wide pH range, (Fig. 11c).

Although, compared with normal cells, many types of tumor cells have higher intracellular H\(_2\)O\(_2\) levels, the endogenously generated H\(_2\)O\(_2\) is still inadequate to obtain improved CDT efficacy [115]. Thereafter, their anticancer efficiency could be enhanced by the introduction of H\(_2\)O\(_2\)-supplementing functionality into CDT agents. Lin et al. developed copper peroxide nanodots for H\(_2\)O\(_2\) self-supplying chemodynamic therapy [116]. Copper peroxide CP nanodots were prepared through the binding of H\(_2\)O\(_2\) to Cu\(^{2+}\) in the presence of poly(vinylpyrrolidone) (PVP) as stabilizer at room temperature. This Fenton-type peroxide nanomaterial utilized as an activatable agent for enhanced CDT by self-supplying H\(_2\)O\(_2\) (Fig. 12a). Upon acid treatment, the reversible decomposition of CP nanodots into Fenton catalytic Cu\(^{2+}\) and H\(_2\)O\(_2\) occurred.

2′,7′-dichlorofluorescin diacetate (DCFHDA), the fluorescent ROS indicator, was applied to evaluate the production of OH\(^{-}\) by CP nanodots at the cellular level. Deacetylation of DCFH-DA and formation of nonfluorescent DCFH was accomplished by intracellular esterases, which can be oxidized by ROS and then emits green fluorescence [117]. It was shown in Fig. 12.B that U87MG cancer cells incubated with CP nanodots exhibited significantly higher green fluorescence than untreated control cells, indicating the ability of CP nanodots to generate OH\(^{-}\) within tumor cells.
Therapeutic selectivity, characteristic differences between healthy and cancer cells, is one of the critical factors in development of cancer therapies. Due to rapidly proliferating, cancer cells have high $\text{H}_2\text{O}_2$ levels with a low catalase level in comparison with normal cells. In this regard, SnFe$_2$O$_4$ nanocrystals were employed for selective killing of lung cancer cells by catalase-modulating heterogeneous Fenton reaction [118]. A working mechanism of this developed assay is the inhibition of the heterogeneous Fenton reaction in normal cells with catalase through decomposition of $\text{H}_2\text{O}_2$ (Fig. 13a). Furthermore, the sonicated SnFe$_2$O$_4$ nanocrystals demonstrated much higher efficiency than the non-sonicated nanocrystals to produce the hydroxyl radicals. Therefore, the sonicated SnFe$_2$O$_4$ nanocrystals in presence of catalase exhibited low cell viability compared with test cells treated with non-sonicated nanocrystals without catalase (Fig. 13b).

In cancer therapy, DOX can activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) for transportation of electrons across the membrane. The activated NOXs can catalyze NADPH into NADP$^+$ along with the release of electrons. Thus, the oxygen captures the electrons to produce the superoxide anion radical ($\text{O}_2^{-}$) and afterward product the $\text{H}_2\text{O}_2$ by disproportionation reaction with superoxide dismutase (SOD) enzyme.
In Fenton reactions, iron oxide core–shell mesoporous silica (Fe₃O₄@MSN) nanocarrier promoted oxygen species levels reactive for cancer therapy [122]. Fe₃O₄@MSN-TPP/PEG-FA was formed by conjugation of Fe₃O₄@MSN with folate (PEG-FA) and mitochondrial targeting triphenylphosphonium (TPP). Then, Fe₃O₄@MSN-TPP/PEG-FA encapsulated doxorubicin (DOX) and 3-amino-1,2,4-triazole (AT) for cancer therapy (Fig. 14I). AT, as a catalase inhibitor inhibits the catalase activity to save the production of H₂O₂. The assessment of ROS level induced by DOX/AT-loaded Fe₃O₄@MSN-TPP/PEG-FA in MCF-7 and MGC-803 cells showed that green fluorescence was gradually improved after different incubation times (Fig. 14II). The results proved the significant elevation of the intracellular ROS level stimulated by DOX/AT-loaded Fe₃O₄@MSN-TPP/PEG-FA.
Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is the most versatile minimal invasive manner of cancer therapy, which involves the production of cytotoxic reactive oxygen species (ROS) by light activation of photosensitizers [123, 124]. The produced ROS induce cell apoptosis or necrosis, microvascular damage and immune responses. Aggressive proliferation of cancer cells and an insufficient blood supply in tumors decrease O₂ concentration. The O₂ deficiency in tumors leads to a significantly reduced antitumor efficacy of PDT [125–127]. In PDT, O₂ employs to produce ROS, so, hypoxia obviously arises during PDT. Hypoxia, yielded from the imbalance between oxygen supply and consumption, is a great indicator of cancer progression. Since, O₂ is a necessary component in PDT and hypoxia prevents effective cancer treatments [128, 129]. In view of this, tremendous attention has been attracted to overcome tumor hypoxia. Recently, various nanomaterials with catalase like activity, have been employed to catalytically generate O₂ to mitigate cancer hypoxia. For example, manganese ferrite nanoparticle-anchored mesoporous silica nanoparticles to eliminate hypoxia and efficient photodynamic therapy [130]. Manganese ferrite nanoparticles (MFNs) act as a Fenton catalyst for decomposition of H₂O₂ and continuous O₂ generation. The level of hypoxia can be examined based on HIF-1α amounts, because hypoxia-inducible factor (HIF-1α) protein is adjusted under hypoxic condition [131]. As can be seen in Fig. 15, when the cancer cells were treated with manganese ferrite nanoparticle-anchored mesoporous silica nanoparticles (MFMSNs), the fluorescence intensity of HIF-1α has decreased in concentration dependent manner, suggesting the capability of MFMSNs to reducing hypoxia via O₂ production after cellular uptake.

In another study, Zhang et al. used MnO₂ nanodots to promote dissolved oxygen concentration and overcome hypoxia limitations [132]. The PDT nanoplatform is fabricated by one-pot encapsulating g-C₃N₄ and DOX in ZIF-8, then loading MnO₂ nanodots and surface-modifying F127 (F127-MnO2-ZIF@DOX/C3N4, donated as FMZ/DC). F127 with excellent biocompatibility and amphiphilic nature is chosen as a stabilizing agent. Encapsulation into pH-dependent ZIF-8 carrier reduces the side effects of DOX induced by nonspecific drug release. In addition, g-C3N4, a prominent visible-light photocatalyst, could efficiently generate ROS and kill cancer cells (Fig. 16a, b). The efficacy of the tested materials to the living body was confirmed by measuring the tumor sizes of mice during the healing process (Fig. 16c, d).

MnO₂ biomimetic nanozyme could be integrated glucose oxidase (GOx) enzyme for improved starvation and photodynamic therapy [133]. GOx can oxidize glucose to gluconic acid and H₂O₂, which is capable of tumor starvation therapy. Meanwhile, MnO₂ accelerated O₂ production with the aid of a large amount of H⁺ from oxidation product gluconic acid. This O₂ supply decreases tumor hypoxia and promotes PDT effectiveness (Fig. 17).

To achieve more stability and hinder the aggregation of small size mimicking enzyme nanoparticles, Zhang’s group decorated Pt nanozymes on photosensitizers integrated MOFs for enhanced photodynamic therapy [134]. Pt nanoparticles with catalase like activity were decorated on porous coordination network-224 (PCN-224). The PCN-224-Pt could assist the formation of 'O₂ in hypoxic tumor site via decomposition of H₂O₂ for producing O₂, which could be employed for enhanced photodynamic therapy (Fig. 18I). Decreased in immunofluorescence intensity of HIF-1α for treated tumor slices with
PCN-224-Pt indicated remove the hypoxia limitation by Pt NPs on PCN-224-Pt (Fig. 1). In the case of tumors of mice injected with PCN-224, tumor growth was completely inhibited after irradiation treatment (Fig. 18II).

It is reported that the activities of enzyme mimics are correlated with their nanostructures [135]. For instance, MoO$_3$–x nanurchins (NUs) exhibited a structure-dependent enzymatic activity with therapeutic effect in tumor microenvironment via cascade catalytic reactions [136]. In this design, MoO$_3$–x NUs possess high proportion of active Mo$^V$ atoms and large active surface area, induce catalase (CAT)-like activity to produce a
large amount of O₂ for subsequent oxidase (OXD)-like reactivity (Fig. 19). The reactivity of MoO₃₋ₓ NUs in acidic PBS is much higher than that in neutral or alkaline; thus, MoO₃₋ₓ NUs would rapidly lose the enzymatic activity and leave normal tissues unharmed in a physiological environment (pH ∼ 7.4).

**Photothermal therapy (PTT)**
Photothermal therapy (PTT) is a treatment modality with minimum side effects, which involves the artificial elevation of the tissue temperature. PTT agents capture near-infrared (NIR) light and convert it into heat, causing
tumor cells apoptosis [137–139]. Without any laser exposure, PTT agents are nontoxic and relatively safe to cells. In compare with traditional tumor treatment models including radiotherapy, surgery, and chemotherapy, PTT is attractive because of certain advantages, such as reduced invasiveness and high specificity [140, 141]. Nevertheless, tumor cells usually cannot be completely killed by photothermal treatment alone, finally resulting in tumor recurrence [142]. Thus, to further enhance the therapeutic performance of PTT, the enzyme-mimicking performance of nanozymes can be employed.

Au nanoparticles (Au NPs) are one of the most widely studied photothermal agents owing to their effective local heating upon excitation of surface plasmon oscillations. Besides, many studies displayed that Au NPs possess enzyme-like activities [143]. In this regard, Fan’s group utilized yolk-shell gold@carbon nanozymes Tumor catalytic-photothermal therapy [144]. A hollow carbon nanospheres with porous shell (Au@HCNs) exhibited high oxidase-like and peroxidase-like activity enzyme activities. Meanwhile, Au@HCNs outstanding near-infrared light (NIR) absorbing agents for convert light into heat for tumor photothermal therapy (PTT). The enzyme-mimicking functions significantly improved by the photothermal effect, leading to large amounts production of ROS to destruct cancer cells. Tumor mice have been exposed with different groups of agents with or without NIR irradiation. The results showed that the tumors treated with Au@HCNs under 808-nm laser irradiation were completely destroyed without recurrence during the treatment (Fig. 20).

Nanoceria (NCeO2) decorated flower-like MoS2 nanoflakes reported as a nanozyme for cancer photothermal therapy (PTT) [145]. Polyethylenimine (PEI) coated flower-like MoS2 nanoflakes surface decorated with cerium oxide NPs to formation of NCeO2-PEI-MoS2. The NCeO2 decoration considerably enhanced the photoconversion effectiveness (PCEs) of MoS2 nanoflakes. The different effects of NCeO2-PEI-MoS2 nanoflakes on cancer and normal cells were due to multi-enzyme mimics of NCeO2. Normal cells protect against oxidative damage via neutralization of free superoxide radicals and hydrogen peroxide by superoxide dismutase (SOD) and catalase enzyme mimic to decompose H2O2 into water and O2. Although, in acidic cancer cell NCeO2 work as a Fenton-like catalyst that dismutates H2O2 to OH. Next, O2·− and H2O2 are formed by dismutating CO2 or ordinary molecular oxygen (O2). The formed.

ROS species (OH·, O2·−and H2O2) induce oxidative stress leading to cell death or apoptosis in cancer cells (Fig. 21).

**Sonodynamic therapy (SDT)**
Ultrasound (US) can penetrate biological tissues, capable of activating sonosensitizers to generate toxic ROS molecules for cancer therapy modality named

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**Fig. 15** a Schematic illustration of MFMSNs. b CLSM images of HIF-1α (green) and F-actin (red) in cells incubated with MFMSN under normoxic or hypoxic condition, and c corresponding fluorescence intensity (n = 3). Scale bar, 20 μm. **P < 0.01
sonodynamic therapy (SDT). SDT can obviate the severe issue of low tissue-penetrating depth of traditional phototriggered therapies, but the SDT efficiency is still not satisfactory in battling cancer [146–148]. In SDT, ultrasound (US) can trigger sonosensitizers to produce ROS, bubbles, cavitation and hyperthermia. It has a good therapeutic effect on the treatment of deep malignant tumors. SDT is a selective method for treatment of deep malignant tumors, because US can precisely focus on the tumor region, target to activate sonosensitizers, and minimize the damage to the adjacent normal organs and tissues [146, 149]. The solid tumor microenvironment (TME) appears when there is critical hypoxia because of O₂ consumption during SDT [150]. Thereby, enzyme mimic nanomaterials can also work as the synergistic agents to boost the therapy.
efficiency by alleviating tumor hypoxia. Nanoenzymes can convert the tumor-overexpressed hydrogen peroxide (H$_2$O$_2$) molecules into oxygen and enhancing the tumor oxygen level to boost SDT-induced ROS production. Liang et al. employed hollow Pt-CuS janus architecture for synergistic catalysis-enhanced sonodynamic and photothermal cancer therapy [151]. Sonosensitizer molecules (tetra-(4-aminophenyl) porphyrin, TAPP) loaded on inner cavities of hollow CuS to fulfillment SDT. Metallic Pt with enzyme like-activity catalyzed decomposition of endogenous overexpressed H$_2$O$_2$ to produce O$_2$ and facilitates SDT efficacy (Fig. 22). Nanozymes can act as a carrier effectively deliver a sonosensitizer to the lesions and also provide a sonosensitizer with rich oxygen by their enzyme activities. It was found that the modification of a sonosensitizer onto Pd@Pt could significantly block the catalase-like activity of Pd@Pt, whereas upon US irradiation, the nanozyme activity was effectively recovered to catalyze oxygen generation [152]. Such “blocking and activating” enzyme activity decreases the potential toxicity and side effects of nanozymes on normal tissues and helps realize controllable, active, and disease-loci-specific nanozyme activity behavior.

**Antibacterial applications**

Infectious diseases caused by bacteria are the most growing global health problem, infecting millions of people every year [153]. Until now, a number of antibacterial materials, such as antibiotics, quaternary ammonium ion, metal ions, and biocides have been developed to counter the growth of dangerous bacteria [154, 155]. However, owing to high cost of the above materials, antibiotic resistance, and complex chemical processing, the provision of alternative antimicrobials is of particular importance [156]. It was found that artificial enzyme mimics are able to function as an antimicrobial against both Gram-positive and Gram-negative bacteria via increasing the transformation of H$_2$O$_2$ into ROS [157, 158]. Chen and coworkers have found that graphene quantum dot/silver nanoparticle (GQD/AgNP) hybrids with peroxidase and oxidase like functions demonstrate high
antibacterial properties against both Gram-negative and Gram-positive bacteria via using oxygen instead of H₂O₂ [159]. The GQD/AgNP hybrids could induce release of ROS to oxidize the lipids in the cell membrane. After distribution of GQD/AgNP hybrids around the bacteria, the surface morphology of the bacteria exhibited an evident conversion from a smooth cell membrane to a roughened and wrinkled appearance, denoting that the cell membrane had been destroyed and lost its original barrier action (Fig. 23I). The oxidation of the lipids in the cell membrane and disruption the cell metabolism result in bacteria death.

Cai et al. also fabricated porous Pt/Ag nanoparticles with excellent multifunctional enzyme mimic to exert excellent antibacterial effects [160]. The multi-catalytic capability of Pt/Ag NPs as oxidase peroxidase and catalase, results in suppression of the bacteria growth (Fig. 23II).

Bacterial biofilms are determined as groups or clusters of bacteria, surrounded by a self-produced matrix of extracellular polymeric substances forming the three-dimensional structure. Bacterial biofilms are associated with health problems and diseases including chronic infections, biofouling of implants, as well as tooth decay and biomedical devices. Biofilms are difficult to destroy, because the biofilm mode of growth exerts the protection effect [161–163]. Tao et al. have also demonstrated intrinsic oxidase and peroxidase catalytic functions of bifunctionalized mesoporous silica-supported gold nanoparticles for biofilm destruction [164]. Treatment with both MSN-AuNPs and H₂O₂ led to breaking down the existing biofilm (Fig. 23III).

Light-absorbing characteristics of nanomaterials have created salient opportunities in applying light to activate nanomaterials for control of biological processes. In particular, combining the use of light as a trigger with the nanozyme activity of nanomaterials offers remarkable potential to control the antibacterial property [165, 166]. Karim's group showed the ability of visible light to work as an external trigger for controlling the antibacterial property of semiconducting CuO nanorods (NRs) [167]. In visible light illumination, the apparent binding affinity of CuO NRs to H₂O₂ increased by over four times in comparison with non-illuminated conditions, (Fig. 23IV). The outcome of this distinct feature is progression in the rate of ROS production, so that, antibacterial efficiency of photoilluminated CuO NRs improved by elevating the OH· radical formation even at low H₂O₂ concentrations.

The surface morphology of nanocomposites has a key role in adjusting their catalytic functions. Thus the enzyme-like activity of metal-based nanomaterials could be controlled by modulating their exposed facets [168, 169]. Along these lines facet-dependent of palladium (Pd) nanocrystals have been demonstrated against Gram-positive and Gram-negative bacteria [170]. The antibacterial performance of Pd nanocrystals against Gram-positive bacteria is the consequence of the extent of their enzyme-like activity, that is {100}-faceted Pd cubes with higher activities destroy bacteria more effectively than {111}-faceted Pd octahedrons. This outcome has been corroborated with the dissociative energy profiles for the O₂ molecule on the Pd {111} and {100} surfaces. The O₂ binding on the Pd {111} facet has adsorption energy of −0.85 eV, whereas for the O₂ on the Pd {100} facet, the value is −1.40 eV, indicating that the Pd {100} facet, present in the Pd cubes, exhibits a stronger affinity for the O₂ molecule.

**Water purification**

Organic dyes are one of the widely used industrial products, which, their inseparable disposal poses serious risks to the environment [171]. Dyes generally cause water contamination and many problems to human health and environment, because they are toxic, mutagenic, carcinogenic and non-biodegradable. Therefore, the removal of dyes from wastewater is indispensable, particularly for securing aquatic life and mitigating the problem of water pollution [172, 173]. Among different removal technologies available for the removal of dye-containing wastewater, advanced oxidation processes (AOP) has been suggested as an excellent strategy [174, 175]. Fenton process as one of the advanced oxidation technologies is a strong catalytic reaction used for environmental restoration. In Fenton chemistry, H₂O₂ is decomposed by soluble Fe³⁺ ions to produce highly oxidative species, i.e., hydroxyl radicals, according to the Haber–Weiss mechanism in Eq. (1) [176, 177]:

\[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^- + \text{OH}^- \]

The homogeneous Fenton process based on the aqueous mixture of iron ion (Fe²⁺/Fe³⁺) and hydrogen peroxide (H₂O₂) suffers from sludge formation and pH...
Figure 1: (a) Schematic representation of the preparation of Pt NPs in suit growth with HOOC-PEG-COOH. (b) Mechanism of cell death induced by Pt NPs.

Figure 2: (a) HIF-1α expression in control and PCN-224-treated groups. (b) Tumor growth in different groups at 0 and 14 days. (c) Representative images of tumor slices. (d) Graph showing relative tumor volume over time.
limitations. Hence, much attempt has been devoted to the development of heterogeneous Fenton catalysts to address these issues [178, 179]. In that respect, iron oxide nanocomposite has attracted much interest for their applications in catalytic degradation of organic pollutants with H$_2$O$_2$ [180, 181]. Various forms of iron oxides such as Fe$_3$O$_4$, Fe$_2$O$_3$ and CuFe$_2$O$_4$ have been used as catalysts to activate H$_2$O$_2$ and generate ROS to remove of organic pollutants [182–184]. However, long reaction time and high concentration of H$_2$O$_2$ are the limitations of the H$_2$O$_2$-iron oxide catalytic system [185]. Therefore, the peroxidase-like activity of catalyst should be enhanced. Transition metal substituted magnetite could be introduced to improve the degradation of organic pollutants via Fenton reaction [186]. It was found that the degradation of methylene blue could be significantly improved through incorporation of niobium with magnetite catalyst. This ascribed to the generated oxygen vacancies on the surface of catalysts. Fe$^{2+}$ cations were regenerated by introduction of Nb cations in Fenton oxidation cycle [187]. An ionothermal synthesis approach has been reported to generate Fe$_3$O$_4$ MNPs with unique intrinsic catalytic activity. In this synthesis strategy a deep eutectic solvent (DES) was applied for Fe$^{2+}$/Fe$^{3+}$ co-precipitation. As compared to Fe$_3$O$_4$ particles prepared in conventional commonly used solvents (water and ethyleneglycol), Fe$_3$O$_4$ MNPs made in DES possessed the higher activity for catalytic degradation of Rhodamine B (RhB) [188]. Utilization of some other Fenton catalyst was investigated for degradation of the organic dyes. Application of nanoceria, with excellent structural properties and high oxygen mobility, was studied for the removal of organic dyes. The proposed mechanism of Fenton-like reaction catalyzed by nanoceria is the activation of H$_2$O$_2$ by Ce$^{4+}$/Ce$^{3+}$ sites and then decompose into highly reactive hydroxyl radicals [189].
Fig. 20  In vivo catalytic-photothermal therapy of CT26 tumor bearing mice. a IR thermal images of CT26 tumor-bear mice with the NIR laser irradiation (808 nm, 2.0 W/cm², 10 min) after intravenous injection with PBS, HCNs and Au@HCNs. b Tumor growth curves of different groups after treatment. c The body weight after various treatments during 21 days. d Photos of tumors from (1) control, (2) HCNs, (3) Au@HCNs, (4) HCNs + Laser, (5) Au@HCNs + Laser. e The Tumor weight after 21 days of treatment. f Representative photos of tumors on mice after various treatments after 21 day
**Summary and prospect**

Since the discovery of Fe₃O₄ nanoparticles as peroxidase mimics in 2007, nanozymes as novel emerging and rapidly growing field have gained much attention. In this regard, metal and metal oxide nanomaterials are a good candidate to replace some complicated and expensive enzymes for using them as a novel and unique techniques in various areas such as bio nanotechnology and environmental governance. In comparison with natural enzyme, nanozymes encompasses many advantages including easy preparation, excellent stability, low cost, and good durability. In this review, we have summarized the recent achievements in application of metal and metal oxide-based nanozymes, including sensing, therapeutics, antibacterial application and water treatment. Obviously substantial progress has been achieved in research field of nanozyme; however, there are still numerous challenges remain to be addressed. First, the diversity of nanozymes is very low compared to natural enzymes; in other words, though many nanomaterials have been applied to mimic natural enzymes. Currently the redox enzyme mimics are still prevailing in the peroxidase-like nanozymes. Thus, new strategies are required to design and prepare other types of nanozymes. Second, in comparison with natural enzyme, nanozymes should provide a competitive catalytic selectivity and efficiency for practical applications. The surface modifications of nanomaterials by functional groups to make the active site for
substrate recognition can boost the binding affinity and specificity of nanozymes. Furthermore, designing hybrid nanomaterials with synergetic effect can help to improve their activity. Third, in general, the developed nanozymes just have one enzymatic activity. The researchers need to pay more attention to construct nanozymes which catalyze cascade reactions to mimic the complex natural enzyme systems. Forth, although nanozymes offer cost-effective methods for application in various fields, noble metal nanomaterials (Au, Pt and Pd) don’t take advantage of low cost. Therefore, the efforts should be propelled to synthesis and application of non-noble nanozymes as low cost and available materials. Fifth, potential toxicities of nanozymes should be carefully considered for biomedical applications. Sixth, the current research on applications of nanozymes are mainly limited to medicine and biotechnology. Future research should be focused on widening the practical applications of nanozymes in other fields including food, industry, agriculture or environment. The spread of the novel coronavirus disease (COVID19) has been a challenge that requires an emergent deployment of diagnostic and therapeutic options available. Development of a simple and sensitive immunodiagnostic method based on nanozymes can be useful for monitoring COVID19. Recently, a nanozyme chemiluminescence immunosensor for rapid and portable detection of SARS-CoV-2 spike antigen (S antigen) is developed [109]. The test paper platform based on a peroxidase nanozyme combines traditional enzymatic chemiluminescence analysis (CLIA) with lateral flow assay, which, facilitates...
early screening of SARS-CoV-2 infections. Furthermore, nanozymes possess the antiviral activity through catalyzing lipid peroxidation of the viral lipid envelope. Thus, nanozymes have the ability to prevent COVID19 transmission and infection.

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