Nanozymes-recent development and biomedical applications

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Abstract
Nanozyme is a series of nanomaterials with enzyme-mimetic activities that can proceed with the catalytic reactions of natural enzymes. In the field of biomedicine, nanozymes are capturing tremendous attention due to their high stability and low cost. Enzyme-mimetic activities of nanozymes can be regulated by multiple factors, such as the chemical state of metal ion, pH, hydrogen peroxide (H2O2), and glutathione (GSH) level, presenting great promise for biomedical applications. Over the past decade, multi-functional nanozymes have been developed for various biomedical applications. To promote the understandings of nanozymes and the development of novel and multi-functional nanozymes, we herein provide a comprehensive review of the nanozymes and their applications in the biomedical field. Nanozymes with versatile enzyme-like properties are briefly overviewed, and their mechanism and application are discussed to provide understandings for future research. Finally, underlying challenges and prospects of nanozymes in the biomedical frontier are discussed in this review.

Keywords: Nanozyme, Oxidative stress, Reactive oxygen species, Disease therapy

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Background
Nanozymes, as artificial enzymes, are nanomaterials with enzyme mimetic activities, which have attracted considerable interest due to their relatively higher physiochemical stability against harsh environments, higher durability, and lower costs than natural enzymes [1]. In the past decades, numerous nanomaterials have been revealed to elucidate the oxidase (OXD), glucose oxidase (GOD), peroxidase (POD), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) mimicking activities with extensive biomedical applications [2, 3]. At present, nanozymes are mainly composed of metal and metal oxides, since the metallic active center can effectively mimic the catalytic electronic redox process enabled by natural enzymes. Specifically, the enzyme-mimicking activities are affected by various factors, such as the oxidation states of the metallic center, reduction agent, temperature, and pH in the surrounding environment [4, 5]. Interestingly, the disease features differ from normal tissues provide typical therapeutic options for rational design and application of nanozymes in biomedicine. It is well known that the tumor microenvironment (TME) exhibits higher redox potential levels than the normal tissues. Such characteristics in the tumor can catalyze enzyme-like activities of the nanozymes [6–8]. For instance, metallic ions (such as Fe^{3+}, Cu^{2+}, and Mn^{4+}, etc.) can be reduced to lower-valent metallic ions (Fe^{2+}, Cu^{+}, and Mn^{3+}) by intracellular GSH [9–11]. Hence, the POD activities and catalytic efficiency of the nanozymes could be altered remarkably in the specific pathological microenvironment.

Although numerous nanozymes having been made in the biomedicine field, it is still challenging to obtain a fundamental insight into the key factors that affect the
catalytic performance, enzymatic-likes properties, as well as the substrate selectivity of nanozymes, on the basis of the interplay between intrinsic structure and extrinsic environment \[12, 13\]. Moreover, the catalytic mechanisms of metal oxide nanozymes are pivotal to rationally design novel nanozymes with inherent catalytic capacities and this approach has been widely applied in biomedicine as a controllable multifunctional platform \[14, 15\]. Recently, many types of nanoparticles with inherent catalytic properties have been reported to achieve various biomedical applications, including oxygen-dependent tumor therapy, radiotherapy, chemodynamic therapy, bacterial infection diseases, and reactive oxygen species (ROS)-related diseases, etc. \[16–20\]. Therefore, recent advances in the field of nanozyme’s biomedical application may bring new insights into the popularization of nanoparticles in the treatment of the biomedical field.

In this review, Different metal- or metal-based nanozymes have been overviewed and described as classified according to their catalytic active center, which significantly impacts the functionalities and activities of the nanozymes during certain catalytic reactions. The versatile enzymes-like properties, mechanism of nanozymes, and the factors that affect the catalytic performance are initially summarized. Then, recently administrated strategies of nanozymes in the therapeutic frontier have been introduced (Scheme 1). Finally, the current challenges of the development of nanozymes and prospects are discussed. We hope that the present review will be of significant benefit for different biomedical fields and provide insightful ideas for the design and development of nanozymes.
Cerium-based nanozymes

Cerium (Ce)-based nanoparticles have been exploited for biomedical applications since they exhibit multiple enzyme-like activities such as catalase- (CAT), peroxidase- (POD), cytochrome c oxidase-, and superoxide dismutase-mimetic (SOD) functions [21–23]. The underlying mechanism of nanoceria-mediated enzymatic reactions was associated with the chemical state of the cerium element. The reduction state \( \text{Ce}^{3+} \) and oxidation state \( \text{Ce}^{4+} \) affect the enzyme-like performance of \( \text{CeO}_2 \) [24, 25]. Singh et al. reported that \( \text{CeVO}_4 \) nanoparticles exhibited cytochrome c oxidase (CcO) activity, which can dismutase oxygen into water at physiological pH conditions due to the electron transfer between \( \text{Ce}^{3+}, \text{Ce}^{4+}, \text{and} \ V^{5+} \) [26]. Interestingly, the ratio of \( \text{Ce}^{3+}/\text{Ce}^{4+} \) of \( \text{CeVO}_4 \) has been shown to affect the CcO-like activity of \( \text{CeVO}_4 \). The authors suggested that the lower ratio \( \text{Ce}^{3+}/\text{Ce}^{4+} \) had higher CcO-like activity in \( \text{CeVO}_4 \) while the higher ratio of lowered valence states (\( \text{Ce}^{3+} \)) corresponds to the higher SOD-like activity. The present study demonstrated the enzyme-mimetic activities of Ce-based nanozymes associated with available oxidation states. Importantly, recent studies manifested that the surface defect characteristics of \( \text{CeO}_2 \) could partly affect the enzyme-like capability. Recently, Wang et al. revealed the SOD- and CAT mimicking mechanisms of \( \text{CeO}_2 \) by first-principles calculations [27]. Their results suggested that oxygen vacancies played critical roles to scavenge superoxide anion (\( \text{O}_2^{-} \)) and hydrogen peroxide (\( \text{H}_2\text{O}_2 \)). The oxygen vacancies impacting enzyme-mimetic activities were mainly ascribed to the reduced activation energy and the formation of the intermediate species. This research suggests that the reduction of activation energy by \( \text{CeO}_2 \) is critically important in exploring the catalytic processes. Their catalytic activity is substantially affected by the intrinsic properties (e.g., dimensions, oxygen vacancy) and physiological factors such as pH, GSH, and temperature. Meanwhile, the oxygen vacancy concentrations were highly dependent on the particle size of \( \text{CeO}_2 \) [28].

Despite the advancements made in biomedicine, nanoceria has key limitations that need to be overcome. For instance, the precise regulation of the enzyme activities remains challenging for nanoceria to meet the biomedical application. Moreover, the toxicity of nanoceria against normal tissues still presents great challenges in achieving clinical application. Previous studies have explored the toxicity effect of \( \text{CeO}_2 \) of varied shapes in RAW264.7 cell line. Compared with the cubic/octahedral morphological nanoparticles, the rod-like CeO2 shows increasing serum concentration of tumor necrosis factor alpha (TNF-\( \alpha \)) and lactate dehydrogenase (LDH) release, demonstrating the morphological-dependent cytotoxicities [29]. The biocompatibility of \( \text{CeO}_2 \) nanoparticle was demonstrated in further in vivo studies in rats when administrating \( \text{CeO}_2 \) of as high as 20 mg/kg [30]. These observations provide an important inspiration for other nanozyme to achieve higher therapeutic effect with minimal toxicity. To solve the low selectivity and poor therapeutic effects, it is highly appealing to design controllable nanoceria-based therapeutic systems. Noteworthily, the catalytic behavior of nanoceria is also determined by physiologically catalytic environments. By controlling enzyme activities in a TME or light stimuli, a desired therapeutic effect with low tissue damage could be achieved. Zhu et al. reported that the self-regulated nanoceria-doped poly-(cyclopentadithiophene-alt-benzothiadiazole) (SPN-C23) as smart nanoplatforms for tumor photodynamic therapy (PDT) [31]. When near-infrared (NIR) laser was irradiated against the tumor tissue with acidic microenvironment (pH=6.5), SPN-C23, acted as a ROS converter, was able to amplify PDT damage against tumor tissues through catalyzing \( \text{O}_2^{-} \) to produce \( \text{H}_2\text{O}_2 \) (Fig. 1A). When exposed to the normal microenvironment (pH=7.4), \( \text{Ce}^{4+} \) of SPN-C23 could transform \( \text{O}_2^{-} \) to \( \text{O}_2 \) with generated \( \text{Ce}^{3+} \) due to oxygen vacancies in the surface of nanoceria. Consequently, SPN-C23 exhibited high singlet oxygen sensor green (SOSG) fluorescence enhancement at pH=6.5 and possessed relatively low fluorescence intensity at pH=7.4 (Fig. 1B), demonstrating that pH-dependent single oxygen species (\( \text{O}_2 \)) production of SPN-C23. SPN-C23 also possesses higher fluorescence at pH=6.5 and NIR laser irradiation, indicating that the generation of \( \text{H}_2\text{O}_2 \) (Fig. 1C). PDT efficiency of SPN-C23 was evaluated on in vivo 4-T1 xenograft tumor model. Under NIR laser irradiation, the growth of the tumor in SPN-C23 treated group was significantly suppressed after intravenous injection of SPN-C23 for 16 days (Fig. 1D). Tissue damage by SPN-0 and SPN-C23 were examined by histological (H&E) staining respectively. The damaged area of the healthy muscle tissues in the SPN-C23 group was significantly decreased as compared to the SPN-0 treatment group (Fig. 1E). Their study provides an effective approach by utilizing ceria-based nanozyme to regulate PDT against cancer with high biocompatibility.

ROS as the signaling messengers play an essential function in the physiological signal transduction pathway [32]. Endogenous and low concentrations of ROS can be produced from normal metabolic processes in the living cells [33, 34]. However, ROS are highly toxic at higher concentrations and can damage protein, RNA, and DNA, leading to cell death [32, 35]. Therefore, ameliorating the oxidative stress induced by ROS has been proved to be beneficial in pathological therapy, such as age-related macular degeneration (AMD), traumatic brain injury,
and ischemic disease [23, 36–38]. Nanoceria is often employed as an antioxidant agent to treat ROS-relevant diseases. For instance, AMD is associated with irreversible ROS damage against the macular that may lead to blindness [39, 40]. Generally, evidence showed that AMD pathology can be treated by counteracting the overproduction of ROS. Mitra et al. reported a nanoceria with dominated $\text{Ce}^{3+}$ that can scavenge the ROS, such as $\text{H}_2\text{O}_2$ and $\cdot \text{OH}$, and inhibit neovascularization formation [41]. Moreover, Yan et al. developed a single-atom Pt/CeO$_2$ for traumatic brain injury treatment [36]. Compared with CeO$_2$, Pt/CeO$_2$ exhibits highly enzymatic activity that can scavenge $\text{O}_2^{\cdot -}$, $\cdot \text{NO}$, and $\cdot \text{OH}$. Furthermore, in vivo administration of Pt/CeO$_2$ to C57BL/6 mice can significantly improve the wound recovery by up to 100%, higher than the mice in the untreated group with 50% of the wound closure. Similarly, ischemic stroke is one of the inflammations associated with excessive ROS generation. With excellent antioxidation activity, ceria nanozymes have been applied for efficient treatment of reperfusion-induced injury in ischemic stroke [42]. Although nanoceria with ROS eliminating ability can protect the cells from ROS damage, physiological stability and biocompatibility remained a challenge towards further clinical prospects. Regarding the present issue, He et al. designed a multifunctional nano-system for treating ischemic stroke with prolonged blood circulation time and higher biosafety [43]. CeO$_2@$ZIF-8 were prepared by in-situ capping of
CeO\textsubscript{2} with zeolitic imidazolate framework-8 (ZIF-8) (Fig. 2A). In their design, ZIF-8 was served as peroxidase to maintain the activity of CeO\textsubscript{2}, as well as to enhance the penetration and accumulation of CeO\textsubscript{2} to brain tissue. In PC12 neuronal cells, CeO\textsubscript{2}@ZIF-8 can effectively protect cells from tert-butyl hydroperoxide (t-BOOH) induced cell apoptosis (Fig. 2B). In vivo administration of CeO\textsubscript{2}@ZIF-8 could significantly reduce the infarcted area and increased the neurological scores of mice, confirming that CeO\textsubscript{2}@ZIF-8 can effectively treat mice with ischemic stroke (Fig. 2C, D).

Another interesting application of nanoceria was the elimination of extracellular DNA (eDNA) for anti-biofilms. Biofilms, a community of bacteria cells, prevents a majority of approaches to treat bacterial infectious diseases in humans. eDNA is a crosslinking component of bacteria biofilm, which provides a potential survival benefit for bacterial infection. It has been established that eDNA has a profound impact on the process of biofilm formation. Therefore, eradicating eDNA is an effective strategy to treat biofilm infection. Functionalization of CeO\textsubscript{2} offers a versatile approach in combating biofilm formation and bacterial infection. Liu et al. designed metal–organic framework (MOF)/Ce-based nanozymes to combat biofilms [44]. The MOF/Ce nanozymes with DNase mimic activities could not only inhibit the biofilm formation but also eradicate established biofilm matrix components by hydrolyzing eDNA. As compared to primitive MOF, MOF/Ce nanozymes possessed higher bactericidal activity via co-incubation. The mechanism

Fig. 2  A Fabrication methodologies and therapeutic mechanism of CeO\textsubscript{2}@ZIF-8 nanozymes. B The viability of PC12 cells co-treated with t-BOOH and nanozymes for two days. C Infarct areas of various groups after treatment (n = 4). D Neurological scores of different groups with CeO\textsubscript{2}@ZIF-8 therapy for three days (n = 10) [43]. Copyright the Authors 2020.
of the bactericidal activity of MOF/Ce nanozymes is that two adjacent Ce⁴⁺ could bind to the oxygen atom of the phosphate group by withdrawing the electrons, resulting in phosphodiester linkage cleaving [45].

**Ferrum-based nanozymes**

Ferrum (Fe)-based nanoparticles have gained extensive attention for various biomedical applications due to their magnetic resonance imaging (MRI) performance, POD-mimetic activity, and CAT mimetic properties [46, 47]. Huo et al. reported that Fe₂O₃ nanoparticles and GOD co-encapsulated into the mesoporous silica nanoparticles could be effective for tumor catalytic therapy [48]. The intrinsic POD-mimetic activity of Fe₂O₃ could generate a considerable amount of ·OH from H₂O₂ produced by the GOD catalysis from glucose. Importantly, the efficiency of ·OH production efficiency involving the amount of Fe²⁺. Compared with the reaction kinetics of Fe³⁺ with H₂O₂ (40–80 L mol⁻¹ s⁻¹), the reaction rate of Fe³⁺ (9.1 × 10⁻⁷ L mol⁻¹ s⁻¹) with H₂O₂ is relatively low [49, 50]. In addition, several reports have established links between POD-mimetic activity and CAT mimicking property of Fe₂O₃ under various conditions. Gao et al. investigated the catalytic mechanism of Fe²⁺/Fe³⁺ proportion in Fe₂O₃ with the use of either a reducing agent (NaBH₄) or an oxidizing agent (NaIO₄) [51]. They found that increased Fe²⁺/Fe³⁺ proportion of Fe₂O₃ could be achieved by NaBH₄ treatment, with the correspondingly enhanced peroxidase-like activity of Fe₂O₃. On the contrary, decreased proportion of Fe²⁺/Fe³⁺ treated by NaIO₄ reduces the POD-like activity of Fe₂O₃. In addition, the authors showed that the pH, temperature, and dimension of nanoparticles could effectively influence the enzyme-like activity of the Fe₂O₃. These pieces of evidence provide insights into the metallic species and their impacts on the enzyme activities of Fe₂O₃. Another study by Wang et al. showed that reducing agents in the physiological environment (L-cysteine/NADPH) can restore Fe³⁺ to Fe²⁺ on the surface of Fe₂O₃, enhancing the abilities of ·OH generation by Fe₂O₃ [52]. To further understand the impact of the physiological environment, Chen et al. investigated the enzymes-like properties of Fe-oxide (Fe₃O₄ and γ-Fe₂O₃) nanoparticles at the cellular level by electron spin resonance (ESR) and multi-parameter water quality meter [53]. They demonstrated that Fe₃O₄ and γ-Fe₂O₃ nanoparticles exhibit higher POD-like activities at pH = 4.8, while CAT-like activities were observed at pH = 7.4. The controllable enzymatic activities in targeted microenvironments provide flexibility and high sensitivity for diverse biomedical applications. Owing to the role of reducing agents in enzyme-like activity, it is feasible that the Fe³⁺ is reduced to Fe²⁺ by the over-expressed GSH in tumor tissues, contributing to the elevation of the ROS generation and resultant tumor destruction.

Fe-based nanozyme with CAT-like activity have been reported to broaden the therapy for ROS-involved cerebral malaria. Zhao et al. designed and synthesized recombinant human ferritin (HFn) modified Fe₂O₃ (Fenozyme) with blood–brain barrier crossing and ROS-scavenging activity to treat cerebral malaria [54]. From the in vivo murine cerebral malaria experiment, it has been revealed that fenozyme possessed significant ROS scavenging abilities of Fe₂O₃ and prominent blood–brain barrier crossing performance of HFn. Administration of the fenozyme can significantly ameliorate the lesion of cerebral malaria and enhance the survival rate of infected mice induced by the parasite.

**Copper-based nanozymes**

Copper (Cu) oxide nanomaterials have received significant attention due to their enzyme-mimetic activity [55–57]. The POD-mimetic activity of Cu oxide nanoparticles has focused on ROS production activity by Fenton-like catalysis by Cu⁷⁺ and/or Cu⁰ [58]. Besides, the reaction rate of Cu⁺ with H₂O₂ was higher than Fe²⁺ because the redox potential of Cu²⁺/Cu⁺ is lower, indicating that Cu⁺ exhibited relatively higher POD-like activities than Fe²⁺ [59, 60]. Similar to Fe²⁺, the Fenton-like activity of Cu-based nanoparticles is the potent antitumor agent. In tumor microenvironment mediated therapy, intratumoral reductive agents (such as GSH) can reduce Cu²⁺ to Cu⁺ species, leading to high selectivity and efficiency. For instance, Ma et al. reported copper-amino acid mercaptide nanomaterials (Cu-Cys) with GSH depletion and Cu⁺ production within the tumor microenvironment [60]. After their accumulation at the tumor sites, Cu⁺ species reacted with H₂O₂ and produced sufficient ROS, initiating the tumor apoptosis via a Fenton-like reaction. Besides tumor treatment, the POD-like activity of Cu oxide nanoparticles has been employed as antibacterial treatment. Xi et al. designed Cu/carbon nanomaterials (Cu-Cys) with GSH depletion and Cu⁺ production under H₂O₂-rich environment. The research progress of Cu-based nanozymes shows their promising biomedicine applications in the targeted disease microenvironment.

Regulating the activity of nanozymes by utilizing an external stimulus may be highly desirable. It has been demonstrated that visible light could modulate the antibacterial activity of CuO. Nurul Karim et al. fabricated a CuO-nanorod that exhibits POD-mimic activities, and the enzymes-like activities were controlled by visible
light [62]. Due to the favorable band structure (1.44 eV), CuO exhibit relatively high POD-like efficiency in the presence of light to kill Gram-negative bacteria efficiently. Besides, the Cu₂O nanoparticles can mimic the cytochrome c oxidase activity [63]. It is worth noting that Cu₅O nanoparticles synthesized in the presence of the structure-directing agent phenylalanine (Phe) can mimic multienzyme activities, such as GPx, POD, superoxide dismutase (SOD), and catalase, enabling the ROS scavenging performance for Parkinson’s disease amelioration [64]. The potential mechanism is that Cu₅O could reduce the intracellular ROS levels and alleviating oxidative damages. On the other hand, Korschelt et al. reported a copper hydroxide (Cu(OH)₂) nanoparticle with glycine functionalized (Gly-Cu(OH)₂) that served as SOD mimics, eliminating O₂⁻ radicals generated while smoking [65]. The mechanism of the SOD-like activity by Gly-Cu(OH)₂ was further investigated. They found that the reduction and re-oxidized by Cu²⁺ of Gly-Cu(OH)₂ play a prominent role to eliminate O₂⁻. Importantly, Lin et al. reported an interesting Cu²⁺-tannic acid (TA) complex nanozyme (Cu-TA) that exhibits SOD-like activity and catalase-like activity for ROS scavenging [66]. The high SOD-like activity of Cu-TA was dependent on the coordination of Cu²⁺ and TA, which enhance the redox potential of Cu²⁺. Additionally, the Cu-TA nanozyme can eliminate -OH and decompose H₂O₂ to H₂O. The ROS scavenging efficiency of nanozyme was further investigated after Cu-TA being loaded into the cigarette filter, and the scavenging efficiency was calculated to be 87.0%, 68.9%, and 34.6% of O₂⁻, H₂O₂, and -OH, respectively.

To increase therapeutic benefit and reduce systemic toxicity, it is highly desirable to develop the Cu-based nanoparticles with higher antioxidant activity. Other groups also reported multienzymes-like activities of Cu-based nanoparticles, Liu et al. fabricated ultrasmall Cu₅.₄O nanoparticles with extensive ROS scavenging efficiency and abilities to treat ROS-related disease (Fig. 3) [67]. They demonstrated that Cu₅.₄O could exhibit CAT-, SOD-, and GPx-mimicking for enhanced treatment effect against
various ROS-mediated diseases at extremely magnitude such as acute kidney injury (AKI) (2 µg/mg for treatment in vivo), liver damage (6 µg/mg for treatment in vivo), as well as wound healing. Moreover, pharmacokinetics and biodistribution experiments revealed that Cu₃O possesses highly renal clearance advances and outstanding biocompatibility.

Manganese-based nanozymes
Manganese (Mn)-oxide nanoparticles have been demonstrated with intrinsic activities of POD-, GPx-, CAT-, and SOD-like activities due to the variable Mn valent states [68, 69]. In the presence of Cl⁻/HCO₃⁻ environment, the Mn²⁺ exhibit POD-like property that can decompose H₂O₂ into ·OH for tumor therapy [9, 70]. Similar to Fe³⁺ and Cu²⁺, the GSH could reduce Mn⁵⁺/Mn⁴⁺ into Mn³⁺ in the tumor microenvironment, the depletion of GSH could sensitize the ROS-based therapeutic strategies such as chemodynamic therapy and photodynamic therapy [71–74]. Recently, Fu et al. constructed Mn-doped calcium phosphate nanoparticles with loaded GOD (GOD-MnCaP) for tumor therapy [70]. Under the tumor microenvironment, GOD could catalyze the intracellular glucose into H₂O₂ for Mn³⁺-mediated ·OH generation and glucicic acid for enhanced Mn⁵⁺-mediated reaction (Mn⁵⁺ + H₂O₂ → Mn³⁺ + OH· + OH⁻) [75]. Mn-containing nanomaterials have also been served as CAT-like nanozymes for O₂ generation, capturing widespread attention in O₂ mediated therapeutic strategy [72, 76–78]. The Mn-oxide nanoparticles have been established as ROS scavenging agents for the treatment of oxidation-stress mediated diseases [69, 79, 80]. Decreasing ROS levels is one of the important therapeutic mechanisms for Mn-oxidated nanoparticles. However, the targeted delivery strategies remain a great challenge for current Mn-based nanozymes to meet different disease criteria. Based on these challenges, a material design approach may provide an appropriate option to satisfy such demand. Shi et al. reported the Mn3O₄ encapsulated erythrocyte with T7 peptides functionalization system (Mn₃O₄@nanoerythrocyte-T7) for ischemic stroke protection [81]. After being accumulated into the infarcted sites via T7 peptides targeting, the Mn₃O₄@nanoerythrocyte-T7 can efficiently scavenge the ROS and supply oxygen before thrombolysis stroke, with O₂ supply to the hemoglobin in the erythrocyte after thrombolysis. Selective targeting to ischemic stroke provides an attractive strategy to achieve a strong Mn-based nanozymes therapeutic effect.

Interestingly, the GOD enzyme-like activity of MnO₂ nanosheets was reported by Tang et al. [82]. They synthesized MnO₂ nanosheets (M-NSs) by a one-step wet-chemical method that had high glucose affinity and thermal stability as compared to the natural GOD. Under NIR laser irradiation, M-NSs could achieve the photothermal conversion while the glucose was gradually transformed to glyconic acid and H₂O₂, resulting in glucose deprivation enhanced photothermal therapy. Such inorganic nanozyme with GOD-like activity provides a new strategy for the evolution of glucose deprivation and ROS-mediated cancer therapy.

Molybdenum-based nanozymes
Molybdenum (Mo) nanoparticles have attracted considerable attention as nanozymes [83–85]. There have been many reports regarding the catalytic activity of SOD, CAT, OXD, and sulfite oxidase, etc. [86, 87]. Although Mo-based nanozymes display outstanding enzyme-mimicking performance, it is still difficult to further expand their application to biomedicine. One of the main constraints for the application of Mo-based nanozymes is that these nanozymes carry both antioxidative and oxidative activities simultaneously, and may fail in their application to inhibit oxidative-mediated injury with satisfied outcome. Han et al. synthesized MoO₃-x nanodots with CAT- and SOD- mimic activities for Alzheimer’s disease treatment [88]. However, the OXD-activities should be considered and may affect the therapeutic benefits of MoO₃-x. Considering these issues, new strategies should be developed to design intelligent nanozymes with controlled enzyme activity at specific microenvironments with acidity. Hu et al. constructed MoO₃-x nanourchins (MoO₃-x NUs) with pH-dependent multi-enzymatic activity for tumor-specific therapy (Fig. 4) [89]. Under normal physiological pH environment, MoO₃-x possessed high biocompatibility due to their stimuli-responsive bio-degradation behavior. MoO₃-x exhibits excellent catalase enzyme activity under acidic and high H₂O₂ conditions such as reduce to the high proportion of Mo⁵⁺ atoms. Furthermore, MoO₃-x exhibits OXD-like activity that could convert O₂ by disintegrated endogenous H₂O₂ to O₂•⁻ for tumor-specific catalytic therapy. This research provides a new potential therapeutic strategy to reduce the toxicity of nanozymes by controlling their acidic-responsive behavior.

Cobalt-based nanozymes
Intrinsic multienzyme-like activities of cobalt (Co)-based nanoparticles have been reported [90–92]. Dong et al. reported the CoO₃ possesses the pH-dependent enzyme-like property and the reaction basis is similar to Fe₃O₄ [93]. The CoO₃ showed optimal CAT-like reactivity and SOD-like activity at higher pH conditions (pH ≥ 7.4), and the CAT-like reactivity of CoO₃ was significantly high than Fe₃O₄ at the same conditions. Additionally, CoO₃ exhibits higher POD-like activity.
in an acidic medium (pH = 3.6). The catalyzing efficacy of Co-based nanozyme limits their biomedical application. Thus, improving the enzyme activity of nanozymes may be therapeutically attractive for better antitumor efficacy. Recently, Sang et al. developed a polyethylene glycol decorated PZIF67-AT nanoparticles by combining the multienzyme-like activities of Co-based zeolitic imidazole framework-67 and 3-amino-1,2,4-triazole (3-AT) [94]. In their design, the SOD-mimetic activity of PZIF67-AT initially converts \( \text{O}_2^{•−} \) to \( \text{H}_2\text{O}_2 \) (Fig. 5), subsequently, the production of \( \text{H}_2\text{O}_2 \) was converted to \( \cdot\text{OH} \) by PZIF67-AT for cancer therapy. The CAT-like activity of PZIF67-AT was inhibited by 3-AT through binding of the Co-active center. In addition, the overexpressed GSH in TME could also be depleted by PZIF67-AT. This study offers an insight into nanozymes in the applications of tumor therapy.

**Platinum-based nanozymes**

Tumor hypoxia and overproduced \( \text{H}_2\text{O}_2 \) is the unique feature of solid tumor, which is critical to tumor proliferation and metastasis [95, 96]. Importantly, the therapeutic efficiency of current methods was limited by tumor hypoxia microenvironments, such as photodynamic therapy (PDT) and radiotherapy [97–99]. Unfortunately, oxygen-dependent PDT was severely discouraged due to the low intratumoral oxygen level [100–102]. Fortunately, nanozymes with catalase-like activities could provide a feasible method to improve tumor oxygen-involved therapeutic methods [103, 104]. Based on the catalase-like activity, platinum (Pt) based nanomaterials have been widely applied to decompose the endogenous \( \text{H}_2\text{O}_2 \) to \( \text{O}_2 \), thus relieving tumor hypoxia for tumor therapy, including PDT and radiotherapy [105, 106]. Zhang et al. report a Pt-PCN-224 nano-platform by decorating Pt on PCN-224 [106, 107]. In the overexpressed \( \text{H}_2\text{O}_2 \) microenvironment, Pt is capable of producing \( \text{O}_2 \) for the photosensitizer (PCN-224) during the photosensitization process to form \( ^1\text{O}_2 \), which could remarkably enhance the outcome of tumor PDT. Besides, Li et al. synthesized porous Pt nanoparticles that can absorb X-ray and convert \( \text{H}_2\text{O}_2 \) to \( \text{O}_2 \), improving the radiotherapy efficiency against the malignant tumor [108].

In addition, Pt-based nanozymes could also be used for ROS and inflammation associated with diseases. In another work, Lin et al. synthesized a cascade nanozyme of Pt@PCN222-Mn to realize anti-inflammatory therapy (Fig. 6) [109]. The PCN222-Mn with SOD-like activity can react with endogenous \( \text{O}_2^{•−} \), resulting in superoxide depletion and subsequent \( \text{H}_2\text{O}_2 \) generation. Then the Pt nanoparticles exhibited strong CAT-like performance to catalyze \( \text{H}_2\text{O}_2 \) for \( \text{O}_2 \) generation, thereby benefiting the inflammatory bowel diseases. This research provides the paradigm that the rationally designed nanozymes could have better
cascade enzymatic performance against pathologies in a variety.

**Gold-based nanozymes**
Enzymatic properties of gold nanoparticles (Au NPs) have widespread uses in biomedical applications [110]. Many studies have reported that Au NPs exhibited multiple-enzymes mimicking abilities such as peroxidase-mimetic activity and glucose oxidase (GOD) activity [111–113]. The GOD-like activity of Au nanoparticles can deplete the glucose and generate H$_2$O$_2$, which could effectively consume glucose nutrients and inducing cell starving in tumor tissues. For example, Gao et al. synthesized the Au-containing inorganic nanozyme platform (DMSN-Au-Fe$_3$O$_4$-PEG) [114]. Firstly, Au specifically catalyzes glucose to H$_2$O$_2$, which was reacted with Fenton agent (Fe$_3$O$_4$) to produce highly toxic hydroxyl radicals (-OH) by typical Fenton reaction for tumor suppression. Additionally, the GOD-mimetic activity of Au nanoparticles has been reported to be synergized with CAT-mimetic nanomaterial enhanced tumor therapy efficiency. Liu et al. loaded Pt and Au into the porphyrin metal–organic frameworks (PCN) with folic acid decoration (P@Pt@P-Au-FA) [115]. The authors showed that endogenous H$_2$O$_2$ could be catalyzed by Pt to O$_2$ for enhanced PDT. The oxygen molecules act as the substrate for gold nanoparticles to convert glucose into H$_2$O$_2$, supplying the reactant of Pt repeatedly. Within the oxygen cycle, remarkably consumption of glucose and production of gluconic acid could accelerate the catalytic efficiency and the antitumor efficiency of Au. However, the total O$_2$ level was not increased during this reaction cycle, low
intracellular O2 levels still constrain tumor therapies that are oxygen-dependent.

The elevated GSH level in cancer cells enables tumor cells to maintain redox homeostasis and resistance to overexpression of ROS [116]. Depletion of GSH has been developed as a smart strategy for enhanced chemodynamic therapy, chemotherapy, photodynamic therapy, and radiotherapy [117]. However, redox homeostasis destruction has been rarely reported for cancer treatment. Based on the biochemical reactions between Au and thiol of GSH, Gong et al. synthesized single-atom Au nanoagents with GPx-like activity to amplify mitochondrial ROS for tumor therapy (Fig. 7) [118].

First, single-atom Au was incorporated into carbon dot (CAT-g) as metal centers catalysis of GSH. Then, triphenylphosphine and cinnamaldehyde were further employed to modify CAT-g (MitoCAT-g) to enable the mitochondria targeting ability and ROS generating ability. As a result, MitoCAT-g effectively strengthened the oxidative stress in the mitochondrial of tumor cells and trigger apoptosis for cell death.

Iridium-based Nanozymes

Other CAT-like nanozymes containing metal oxide-based nanomaterials, such as iridium (Ir) based nanoparticles, have been developed for biomedical applications [119, 120]. The mechanism of these metal oxide-based nanozymes was associated with the oxidation valent of metal species. For example, Su et al. investigated the connections between the CAT-like property of PVP-Ir(0) NPs and chemical state, demonstrating that the formation of IrO2 upon exposure to H2O2 enables the PVP-IrNPs to exhibit CAT-like activity [121]. The POD activities of PVP-IrNPs were originated from electron transfer mediators. Zhang et al. demonstrated that PVP-IrNPs can scavenge ROS and reactive nitrogen species...
(RNS) to alleviate AKI [122]. In their work, ultrasmall PVP-IrNPs (1.5 nm) could rapidly accumulate to the kidney after intravenous administration, protecting ROS- or RNS-mediated cellular damage. Furthermore, PVP-IrNPs could be easily excreted to urine by the kidney and exhibit lower systemic toxicity. Besides, Ir-oxide (IrOx) has been reported that acid-activated OXD-like and pH-dependent CAT-like functions for targeted tumor therapies [123]. At neutral normal tissues, the IrOx presented dominantly CAT-like activities. While the POD-like and OXD-like activities were greatly improved along with the gluconic acid generation by GOD catalysis. Importantly, the glutathione (GSH) can be consumed by Ir^{4+}, dramatically reduced antioxidative species and enhanced lethality could be ultimately achieved.

Ruthenium-based nanozymes

Recently, Xu et al. also discovered that ruthenium (Ru)-based nanoparticles with catalase-like activity could be constructed for highly efficient phototherapy against 4-T1 tumors [124]. In their work, RuO_2@BSA was first prepared by alkaline precipitation methods, and
photosensitizer (IR-808-Br₂) was subsequently decorated into the protein shell to form RuO₂@BSA@IR-808-Br₂. First, the RuO₂ possesses high CAT-like activity, endowing IR-808-Br₂ with highly efficient PDT activity. Second, the RuO₂ has photothermal conversion efficiency for PTT. As a result, RuO₂@BSA@IR-808-Br₂ achieves sufficient tumor inhibition by synergistically enhanced efficacy of PDT and PTT. The catalase-mimetic activity of RuO₂ was activated after being exposed to the tumor microenvironment, and immediately convert H₂O₂ to oxygenate the IR-808-Br₂ for the photodynamic process under near-infrared irradiation. Wei et al. reported a multi-functional IrRu-GOD@PEG NPs that could realize tumor starvation therapy and oxidative therapy by chemical catalysis from H₂O₂ to ¹O₂ [125]. Such an oxidative therapeutic strategy through IrRu alloy nanoparticles provides a new insight for tumor therapy.

Recently, the emerging single atom Ru has drawn extensive attention for endogenous O₂ generation. Wang et al. reported an O₂ generation single-atom Ru nano-platform (OxgeMCC-r) to enhance the therapeutic efficacy of PDT by self-assembly in the presence of PVP, Mn/Ru, and Ce₆ (Fig. 8) [126]. Single-atom Ru allows effective O₂ generation at a low concentration of the Ru to overcome tumor hypoxia for ¹O₂-mediated tumor killing.

**Conclusion and outlook**

The fast development and revolution of nanoscience and nanotechnology has broadened extensive research interests for their application in biomedicine. Nanozymes is one of the emerging research frontiers that exhibit great prospects for disease therapy. Herein, we have summarized and discussed the most recent development of nanozymes with their intrinsic therapeutic...
features for versatile biomedical applications. Despite the tremendous advantages of nanozymes in biomaterial applications, some critical issues and challenges are still needed to be considered. (1) The catalytic efficiency of most nanozymes should be further improved, with controllable enzyme-like activity. It is expected that the enzymatic reactions could be highly lesion site-specific, guaranteeing the biocompatibility and therapeutic specificity. To achieve high enzyme-like activity, introduction of the single-atom nanozymes is the most attractive strategy to achieve such issue, owing to their highly dispersion of the catalytic active sites and atomic utilization efficiency. Yet the loading efficiency of the single metal atoms is limited, challenges for the performance advancement of single-atom nanozymes are remained. In addition, rational design of cascade nanozymes may represent a promising strategy to improve the catalytic efficiency. (2) The molecular mechanism of nanozymes with multi-enzyme activities are still not clear. For instance, nanozymes mimicking dual-enzymes of CAT and POD, are supposed to exhibit self-competition performance during biomedical applications (as these enzymes both consume H2O2). The exact molecular mechanism of the electron movements within the metallic species should be further investigated under different conditions. In this regard, disease microenvironment holds great potential to regulate the desired enzymatic performance of specific nanozyme. Numerous studies have demonstrated the feasibility and responsiveness of nanozymes in broad biomedicine applications under characteristic stimuli, such as pH condition, GSH, and light, etc. Another strategy to regulate the specific enzymatic performance of the nanozyme lies in the application of specific inhibitors. (3) The selectivity and specificity of nanozymes should be further improved and optimized. During tumor therapy, although pH- or GSH-responsive nanozymes have exhibited “smart” enzyme-like activities to kill tumor cells, low selectivity and specificity have limited their further applications. To address this dilemma, rationally designed controllable nanozymes are significant to achieve high specificity of its enzyme-mimetic activity against various diseases. Recently, many studies have demonstrated that exogenous stimuli, such as light and ultrasonic, could serve as the trigger to control nanozymes activation. These modalities may provide feasible options to achieve the desired prominent site-specificity. (4) Biocompatibility and biodegradability should be considered. Overcoming the in vivo toxicity of nanozymes during therapeutics is still a barrier toward clinical application. Currently, systemic injection of nanozymes will inevitably cause adverse effect against normal tissues. For metal-based nanozymes, the toxicity is largely associated to the metallic species of the constructed metal-based nanozymes. Although numerous studies have demonstrated the cytoprotective role and biocompatible character of nanozymes, metal ion release is still considered as the possible factor to cause the side impact against normal tissues due to the metal overload. For example, copper or iron overloaded in normal tissue/cells may trigger Fenton or Fenton-like reaction that could severely damage the biomacromolecules as well as the nucleic acids. Therefore, pharmacokinetics of the nanozymes are of critically important during the biocompatibility and biosafety evaluation. The surface tunable properties of nanozymes provide an opportunity to design biosafety agents. Taken into considerations, surface modification is one of the alternative strategies to overcome the limitation of nanozymes. Moreover, considering the ligands of nanozymes could influence therapeutic outcomes, bioavailability, clearance dynamics, and systemic toxicity. From this perspective, it is necessary to carefully choose a suitable ligand and endow nanozymes with higher biosafety.

Abbreviations

GSH: Glutathione; OXD: Oxidase; GOD: Glucose oxidase; POD: Peroxidase; CAT: Catalase; SOD: Superoxide dismutase, GPx: Glutathione peroxidase; TME: Tumor microenvironment; O2·−: Superoxide anion; H2O2: Hydrogen peroxide; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; CcO: Cytochrome c oxidase; TNF-α: Tumor necrosis factor alpha; LDH: Lactate dehydrogenase; SPN-C23: Self-regulated nanoceria-doped poly-(cyclopentadithiophene-alt-benzothiadiazole); PDT: Photodynamic therapy; NIR: Near-infrared; SOSG: Singlet oxygen sensor green; AMD: Age-related macular degeneration; O2: Single oxygen species; AMD: Age-related macular degeneration; ZIF-8: Zeolitic imidazolate framework-8; t-BOOH: Tert-butyl hydroperoxide; eDNA: Extracellular DNA; MOF: Metal–organic framework; MRI: Magnetic resonance imaging; ESR: Electron spin resonance; HFn: Human ferritin; Cu-Cys: Copper-amino acid mercaptide nanomaterials; Ph: Phenylalanine; TA: Tannic acid; M-NSs: MnO2 nanosheets; MnO2− Nus: MnO2− nanochains; 3-AT: 3-Amino-1,2,4-triazole; PCN: Porphyrin metal–organic frameworks.

Authors’ contributions

XR and DC wrote the manuscript, YW, HL, and YZ checked different sections of the manuscript. HC, XL and MH edited the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare no conflicts of interests.
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