MINI-REVIEW

Nanozymes as efficient tools for catalytic therapeutics

Shengda Liu1 | Jiayun Xu1 | Yunpeng Xing2 | Tengfei Yan1 | Shuangjiang Yu1 | Hongcheng Sun1 | Junqiu Liu1

1 College of Material Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou, P. R. China
2 State Key Laboratory of Supramolecular Structure and Materials, College of Chemistry, Jilin University, Changchun, P. R. China

Correspondence
Hongcheng Sun and Junqiu Liu, College of Material Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, P. R. China. Email: sunhc@hznu.edu.cn; junqiu@hznu.edu.cn

Funding information
National Key R&D Program of China, Grant/Award Numbers: 2020YFA0908500, 2018YFA0901600; the National Natural Science Foundation of China, Grant/Award Number: 22001054; the Medical and Health Research Project of Zhejiang Province, Grant/Award Number: 2020KY239; the Hangzhou Overseas High level Talent (Teams) Innovation and Entrepreneurship Program, Grant/Award Number: 4095C5062000604

Abstract
Nanozymes are emerging nanomaterials with ideal enzymatic catalytic performance. The development of nanozymes has been shown clear potential to overcome the limitations of natural enzymes such as troublesome preparation, ease of denaturation, high price, and difficulty of recycling. Since the discovery of magnetic Fe3O4 nanoparticles with intrinsic peroxidase-like activity in 2007, the researches on nanozymes have been booming in the next decade. According to the unique nanoscale effect, nanozymes show prominent catalytic performance, which enables them to be applied in various fields of biomedical engineering. In this review, we mainly focus on the catalytic therapeutics of nanozymes in combating bacteria, cancer therapy, alleviating inflammation and neuroprotection.

KEYWORDS
alleviating inflammation, cancer therapy, catalytic therapy, combating bacteria, nanozymes, neuroprotection

1 | INTRODUCTION

All the life activities are closely related to enzymes. As unique biocatalysts, natural enzymes with the characteristics of remarkable catalytic activity and extraordinary substrate specificity play an essential role in living systems. However, practical applications of natural enzymes have been limited due to their intrinsic shortcomings: (1) as the catalytic activity depends on the three-dimensional structures of the protein molecules, natural enzymes are prone to conformational changes, resulting in denaturation and inactivation when the surrounding environment changes. (2) Natural enzymes are easy to be degraded by proteases, microorganisms and cells, leading to inactivation. (3) At present, the costs of preparation and purification of natural enzymes are still high, which limits their further applications in biomedical fields.1-3

Bionics embodies the intelligence and creativity of human beings. To address these shortcomings of natural enzymes, natural enzymatic substitutes are gradually
explored by biomimetic strategies. Following the wisdom of nature, artificial enzymes have been established by mimicking the catalytic mechanism of natural enzymes and using alternative substances to perform efficient catalysis.\textsuperscript{4,5} In decades, a variety of artificial enzymes, such as macrocyclic compounds,\textsuperscript{6–8} dendrimers,\textsuperscript{9–11} and supramolecular assemblies, have been developed and widely used in multiple fields.\textsuperscript{12–14} However, the catalytic activity of most artificial enzymes is still relatively low and their preparation is more complex. Improving the catalytic efficiency of artificial enzymes and developing more controllable and efficient preparation techniques are the critical problems in this field.

The rise of nanotechnology has provided unprecedented possibilities for the preparation of highly efficient artificial enzymes and nanozymes emerged at this time. The first evidence of inorganic nanomaterials based on Fe\textsubscript{3}O\textsubscript{4} nanoparticles that have intrinsic peroxidase catalytic activity was reported by Yan and colleagues in 2007.\textsuperscript{15} In this work, optimum reaction conditions, kinetics of enzymatic reaction, and catalytic mechanism were systematically studied from the enzymatic point of view and a systematic method was established to characterize the catalytic activity of nanozymes.\textsuperscript{16} This discovery changed the conventional perception of the biological inertness of nanomaterials. Nanozymes have the biological effects inherent in nanomaterials. The unique properties of nanozymes at the nanoscale, such as ultrafine particle size, adjustable catalytic activity, large surface area, and intelligent response to external stimuli endowed them to show admirable catalytic properties in biomedical applications such as catalytic therapeutics. In this review, we give a general overview of the recent progress in the treatment of bacterial infections, inflammation, cancer, and neurodegenerative diseases (Figure 1).

2 | NANOZYMES FOR COMBATING BACTERIA

Up to now, bacterial infectious diseases have become a worldwide problem and a major hidden danger threatening the global public health.\textsuperscript{17} Antibiotics are commonly used as traditional antimicrobial agents. However, antibiotics lead to bacterial resistance and excessive antibiotics cause serious environmental pollution.\textsuperscript{18} Therefore, it is extremely urgent to develop novel antibacterial agents with high efficiency, environmental friendliness, and avoidance of drug resistance. Nanozyme-based biocatalytic systems with the ability to quickly kill super drug-resistant bacteria and remove biofilms have widespread applications in wound healing, dental caries prevention, and other related treatments.

### 2.1 Nanozymes for elimination of resistant bacteria

Based on the peroxidase and oxidase activities of nanozymes, H\textsubscript{2}O\textsubscript{2} or O\textsubscript{2} can be catalyzed into a large amount of free radicals in a short time and the generated free radicals can rapidly kill drug-resistant bacteria with high efficiency. For example, Qu and coworkers showed that catalyzed by graphene quantum dots, the extremely low level of H\textsubscript{2}O\textsubscript{2} was able to generate reactive oxygen species (ROS) to effectively kill \textit{Escherichia coli} and \textit{Staphylococcus aureus} (Figure 2A and B).\textsuperscript{19} The highly effective bactericidal ability was further used to prevent wound infection and promote wound healing. Besides, Qu’s group also demonstrated that another nanozyme, graphitic carbon nitride loaded with Au nanoparticle exhibited a high peroxidase-like activity.\textsuperscript{20} The nanozyme was able to catalyze H\textsubscript{2}O\textsubscript{2} into ROS for killing drug-resistant \textit{E. coli} and \textit{S. aureus} at a physiological level, thereby accelerating the healing of infectious sores. More importantly, in vivo results illustrated that the nanozymes showed a superior bactericidal effect, which was comparable to that of a potent antibiotic, vancomycin. In order to further enhance the antibacterial effect of nanozymes, more synergistic antibacterial strategies with nanozyme-based catalysis have been explored. For instance, Zhao’s group found that polyethylene glycol (PEG)-modified MoS\textsubscript{2} nanoflowers can effectively kill drug-resistant bacteria by catalyzing H\textsubscript{2}O\textsubscript{2} to generate \textit{OH} through the peroxidase-like activity.\textsuperscript{21} Moreover, combined with
the photothermal effect of the nanoflowers, ampicillin-resistant \textit{E. coli} and endospore-forming \textit{Bacillus Subtilis} were mostly killed under the irradiation of near infrared light, and the wound healing was promoted. What’s more, Sung and coworkers discovered that graphene oxide and iron oxide nanoparticle (IONP) composites dealt with methicillin-resistant \textit{S. aureus} effectively through the catalytic and photothermal synergistic effects, with a synergistic bactericidal efficiency of 80\%, which was the highest rate compared to catalytic and photothermal bactericidal efficiency of 35 and 60\%, respectively (Figure 2C and D).\textsuperscript{22} In vivo results showed that the synergistic bactericidal strategy has a remarkable effect on promoting wound healing. At present, the drug-resistant bacteria killed by the catalytic effects of nanozymes mainly include \textit{E. coli} and \textit{S. aureus}. The antibacterial effect on other bacteria and the corresponding antibacterial spectrum needs further exploration.

### 2.2 Nanozymes for disruption of biofilm

Recent researches have shown that biofilm plays a key role in the formation and development of dental caries and periodontal disease. Bacteria utilize nutrients, such as oligosaccharides ingested from the mouth to grow and form biofilm, which produce acids to erode the surface of teeth to form dental caries and trigger periodontal tissue infections.\textsuperscript{23} In the oral biofilm, biological molecules, such as DNAs, proteins, and oligosaccharides, are the main...
components, in which oligosaccharides account for the highest proportion.\textsuperscript{24} Nanozyme-mediated catalytic reaction could degrade these components of biofilm by free radicals induced by nanozymes and mostly kill internal bacteria. For example, Gao and coworkers reported that Fe$_3$O$_4$ nanozymes could catalyze the efficient degradation of biological molecules by H$_2$O$_2$ under acidic conditions, while the components could not be degraded by H$_2$O$_2$ alone.\textsuperscript{25} The investigation of the biofilm of \textit{Pseudomonas aeruginosa} showed that free radicals catalyzed by Fe$_3$O$_4$ nanozymes disrupted the biofilm to eliminate bacteria, and the enzyme-catalyzed antibacterial effect was ten times higher than that treated with H$_2$O$_2$ alone. Moreover, the results of in vitro biofilm and in vivo oral tissues suggested that nanozymes had the effect of removing oral biofilm and preventing dental caries. Interestingly, in vivo results also showed that Fe$_3$O$_4$ nanozymes themselves could inhibit acid-induced hydroxyapatite dissolution, leading to the prevention of teeth demulsification. The above findings demonstrated that peroxidase-like nanozymes based on Fe$_3$O$_4$ have multiple roles in clearing oral biofilms and preventing dental caries. Later on, Qu and coworkers designed a deoxyriboonuclease (DNase)-mimicking nanozyme, which assembled passivated Au nanoparticles and Ce$^{4+}$ onto the surface of Fe$_3$O$_4$@SiO$_2$ core-shell colloid particles.\textsuperscript{26} The composites with DNase-mimetic activity could degrade DNA molecules, in which the active center of the nanozymes was Ce$^{4+}$. Compared with the natural DNase I, the nanozymes have obvious advantages of stability, repeatability, and low cost. What’s more, the extracellular DNA (eDNA) in the biofilm of \textit{S. aureus} could be degraded by coating the nanozyme on the surface. The biofilm studies showed that the nanozymes prevented more than 90% of bacteria from adhering and inhibited the early growth of biofilm. At the same time, the nanozymes also degraded eDNA in matured biofilm and destroyed the integrity of biofilm structure. If antibiotics were matched in the meantime, the efficiency that the antibiotic entered the biofilm and killed bacteria was further facilitated.

Above all, nanozymes have been developed into favorable antibacterial materials through the biocatalytic reactions. The research on antibacterial applications of nanozymes is just started and the related mechanism and application need to be further explored.

3 | NANOZYMES FOR CANCER THERAPY

As one of the most common malignant tumors, cancer has been treated by surgery, chemotherapy, thermal therapy, and photodynamic therapy (PDT). Nanozymes, as a new enzymatic therapy for tumor therapy, can directly kill tumors by virtue of their peroxidase-mimicking properties, or change the tumor hypoxia microenvironment by virtue of catalase (CAT)-like activity to enhance the therapeutic effect.

3.1 | Nanozymes for catalytic therapy

Nanozyme-mediated antitumor strategies take advantage of metabolic molecules, such as H$_2$O$_2$, glutathione, and glucose, as substrates to change the state of ROS in tumors to achieve tumor treatment. For instance, Shi and coworkers envisaged that a versatile strategy for developing cascade catalytic nanomedicine to kill cancer cells by the delicate integration of natural glucose oxidase (GOD) and inorganic Fe$_3$O$_4$ nanozymes into degradable dendritic silica nanoparticles (Figure 3A and B).\textsuperscript{27} In tumors, natural GOD is able to catalyze the decomposition of glucose to generate H$_2$O$_2$ and gluconic acid, and inorganic nanozymes continue to reduce H$_2$O$_2$ into toxic \textit{•OH} through the peroxidase-like activity for killing cancer cells in an acidic tumor microenvironment. In vivo results showed that the cascade catalytic nanomedicine had an outstanding tumor-inhibition effect on 4T1 and U87 cells. In catalytic treatment, most nanozymes cannot catalyze both H$_2$O$_2$ and O$_2$ into ROS at the same time, resulting in the limitation of the therapeutic effect. Shi and coworkers developed a single-atom Cu nanozyme based on N-doped carbon spherical scaffold, which can concurrently catalyze H$_2$O$_2$ and O$_2$ to generate \textit{•OH} and \textit{O$_2^-$}, respectively, for the enhancement in tumor suppression.\textsuperscript{28} The turnover frequency of Fenton reaction of Cu in the single-atom Cu nanozymes was 5000 times higher than that of Fe in the Fe$_3$O$_4$ nanozymes. In vivo results showed that the single-atom Cu nanozymes effectively inhibited tumor growth. The highly toxic ROS produced by nanozymes is effective in tumor treatment. Unfortunately, the self-protective mechanism of autophagy mechanism in tumor cells could reduce oxidative damage, leading to poor therapeutic efficacy. Therefore, Shi and coworkers reported a synergistic antitumor strategy of nanocatalysis and inhibition of tumor autophagy.\textsuperscript{29} In this work, metal-organic framework (MOF) containing Fe with peroxidase-like activity was applied for the generation of \textit{•OH} by H$_2$O$_2$. While chloroquine, a well-known antimalarial agent, was used for the deacidification of lysosomes and the inhibition of autophagy. In vivo results demonstrated that the synergistic treatment of enzymatic catalytic therapy and autophagy inhibition was particularly effective for tumor inhibition.
3.2 Nanozymes for enhanced therapy

Nanozyme-induced changes of the hypoxic microenvironment in tumor by CAT-like activity are able to enhance the therapeutic efficiency. Tumor hypoxia is the main reason for the limitation of radiotherapy (RT) and PDT, which depends on the concentration of O2. To overcome the resistance of hypoxia-associated RT, Yang and coworkers fabricated Au@MnO2 core-shell nanoparticles coated with PEGs as nanomedicines for enhancing the RT efficiency. As a well-known RT sensitizer, Au core can produce charged particles with X-rays for cancer treatment. In the meanwhile, the MnO2 shell with CAT-like activity can trigger the decomposition of endogenous H2O2 in tumor microenvironment to generate O2 for RT. Blood biochemical assays showed that the nanomedicines had
no obvious toxicity to treated mice when the therapeutic dose was four times, indicating that the synthesized nanomedicines had good biocompatibility. In vivo and in vitro results demonstrated that the nanomedicines had remarkable tumor therapeutic efficiency. Later on, Hyeon and coworkers developed mesoporous silica nanoparticles (MSNs) anchored by manganese ferrite (MnFe$_2$O$_4$) nanoparticles (MnFe$_2$O$_4$-MSNs) as nanozymes to overcome the limitation of hypoxia-associated PDT, resulting in the enhanced therapeutic effect (Figure 4A and B). The MnFe$_2$O$_4$-MSNs loaded photosensitizer chlorin e6 (Ce6), they were able to locate to tumor sites according to the enhanced permeability and retention effects. In tumors, MnFe$_2$O$_4$-MSNs nanozymes catalyzed H$_2$O$_2$ to generate O$_2$, and O$_2$ continued to be catalyzed to produce ROS by light activation of Ce6. In vivo and in vitro results demonstrated that MnFe$_2$O$_4$-MSNs loaded Ce6 continuously supplied O$_2$ under physiological condition, leading to simultaneously reducing hypoxia-associated limitation and improving PDT effect.

The existing nanomedicines based on nanozymes have shown excellent therapeutic effect. We expect that nanozyme-based catalytic therapy would become a new generation of therapeutic strategy.

4 | NANOZYMES FOR ALLEVIATING INFLAMMATION

Inflammation is a defensive response of the body to stimulation, usually manifested as swelling, fever, pain, and dysfunction. Besides, inflammation is a symptom before many diseases occur, so timely treatment of inflammation can prevent related diseases caused by inflammation. A great deal of studies have shown that the overexpression of ROS can be considered as an essential indicator of inflammatory response. Therefore, effectively reducing the level of ROS in inflammatory tissues can alleviate inflammation and prevent related diseases at the same time. According to the ability to scavenge ROS, nanozymes with single or multiple enzymatic activities are considered to be highly effective anti-inflammatory agents.

4.1 | Nanozymes for single catalytic anti-inflammatory

Recent studies have demonstrated that nanozymes with single enzymatic activity had outstanding anti-inflammatory effects. For example, Wei and coworkers...
fabricated a MOF nanozyme based on MIL-47(V)-X (X stand for different chemical substituents) with glutathione peroxidase (GPx)-like activity (Figure 5A and B). In all the MIL-47(V)-X nanozymes, MIL-47(V)-NH2 had the optimal performance, which could most efficiently remove in vitro ROS. In vivo results showed that the MIL-47(V)-NH2 nanozymes were effective in mitigating inflammatory responses in ear inflammation and colitis. The above results not only proved that GPx-like nanozymes could be applied in anti-inflammatory treatments, but also verified that the concepts of the structure-activity relationships could be used for designing related therapies based on nanozymes. In addition to GPx mimics, hydrogenase mimics with H2 production can also be applied in anti-inflammation. Sung’s group developed a hydrogenase-like nanozyme, in which chlorophyll a (photosensitizer), l-ascorbic acid (electron donor) and Au nanoparticles (photo-reducing agents) were encapsulated in a liposomal (Figure 5C). Under the irradiation of 660 nm laser, H2 would be produced to reduce -OH by the nanozymes. The investigations of ROS levels and cytokines in inflammatory tissues showed that the light-driven nanozymes effectively reduced oxidative stress and had great potential in alleviating tissue inflammation.

4.2 Nanozymes for cascade catalytic anti-inflammatory

In organisms, enzymes do not operate alone and several enzymes are involved in the same life process. Recently, nanozymes with multiple enzymatic activities have been developed to scavenge ROS for alleviating inflammation. For instance, by introducing of Mn porphyrin with superoxide dismutase (SOD)-like activity and the platinum (Pt) nanoparticles with CAT-like activity into the Zr-based MOF, PCN222, Wei and coworkers successfully synthesized an integrated cascade nanozyme (Pt@PCN222-Mn) that was able to eliminate ROS (Figure 6A to C). With two separate catalytic active sites, the cascade nanozyme was able to simulate SOD- and CAT-like catalytic activities, respectively. The cascade nanozyme based on the MOF structure had both a confinement effect and a hollow structure, leading to the high-efficient synergistic catalysis and the improvement of the transfer efficiency of the substrate. In vivo results showed that Pt@PCN222-Mn-5 had a synergistic catalytic ability to remove ROS, and achieved a superior therapeutic effect on inflammatory bowel disease (IBD) by optimizing the dosage. In addition, in order to simulate the antioxidant enzymatic defense system in life, Qu’s group constructed
a powerful multinanozyme complex system to effectively remove the overexpressed ROS in cells and protect the system from oxidative damage.\textsuperscript{41} $V_2O_5$ nanowires and $MnO_2$ nanoparticles were developed as a cascade nanozyme, in which $V_2O_5$ nanowires exhibited GPx-like activity and $MnO_2$ nanoparticles showed both SOD- and CAT-like abilities. By the connection of polydopamine (pDA), the prepared $V_2O_5@pDA@MnO_2$ nanozymes had the functions of multiple antioxidant enzymes, which could effectively mimic the intracellular antioxidant defense process involving SOD, CAT, and GPx. Moreover, pDA can also be used as an antioxidant for ROS removal. Therefore, nanozymes showed a synergistic effect to scavenge ROS, thereby effectively protecting cell components against oxidative stress induced by ROS. In vivo results demonstrated that the nanozymes effectively reduced the level of free radicals in the ear inflammation of mice and alleviated the adverse effects of inflammation on mice. What's more, Zhang and coworkers discovered that Prussian blue (PB) nanoparticles had peroxidase-, CAT-, and SOD-like activities at the same time.\textsuperscript{42} The multiple enzymatic activities may be according to the mutual transformation between different valence states of Fe, making PB nanoparticles a superb electron transporter. In vitro results showed that PB nanoparticles had admirable free-radical scavenging activity and could effectively reduce the level of ROS in cells. In vivo results demonstrated that PB nanoparticles effectively inhibited or alleviated the inflammatory reaction of hepatitis in mice and played an essential role in body protection. The cascade reaction of nanozymes to eliminate ROS has excellent anti-inflammatory effect. However, due to the lack of specificity in treatment, long-term use may cause problems such as immune response, antibiotic resistance, and multiple complications. By in-situ growth of $CeO_2$ nanoparticles on montmorillonite (MMT), Wei and coworkers successfully synthesized $CeO_2@MMT$ nanozymes targeted therapeutic agents localizing to the inflammatory sites (Figure 7A to C).\textsuperscript{43} $CeO_2$ nanoparticles with powerful ROS scavenging ability were positively charged, which were not specific to the
inflammatory area of the bowel. Moreover, the ultra-small size of CeO$_2$ nanoparticles also made it easy to be quickly absorbed by the gastrointestinal tract with increased associated side-effects. By combining with MMT, the systemic absorption of CeO$_2$ nanoparticles was significantly inhibited, and the potential nanotoxicity was reduced. Meanwhile, negatively charged MMT sheets combined with positively charged CeO$_2$ nanoparticles led to overall negatively charged CeO$_2$@MMT nanozymes, which were able to target positively charged colon lesions. Therefore, CeO$_2$@MMT nanozymes could well reduce bowel inflammation in mice. In vivo results showed that CeO$_2$@MMT nanozymes inhibited diarrhea and hematochezia in mice by eliminating ROS to achieve the reduction of proinflammatory cytokines and the increase of anti-inflammatory cytokines.

In a word, the removal of ROS by nanozymes can effectively alleviate inflammation. By improving the efficiency and safety, nanozymes can be applied for clinical treatments in the future.

5 | Nanozymes for Neuroprotection

Nanozymes have pro-oxidant and antioxidant activities, and their antioxidant activities have a bright application prospect in many neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, and aging. Since all these diseases are related to free radicals, nanozymes with the ability to remove free radicals and regulate ROS levels play an essential role in neuroprotection.
5.1 Nanozymes for Alzheimer’s disease treatment

Alzheimer’s disease is a common neurodegenerative disease that affects thousands of elderly people. Although the pathogenesis of Alzheimer’s disease has not been clarified yet, a large number of studies have shown that the accumulation and precipitation of amyloid beta (Aβ) plaques induced by metal ions are regarded as a vital cause of neuronal dysfunction and apoptosis. Besides, mitochondrial disorder induced by Aβ leads to ROS overexpression is also considered as a possible factor for the initiation of Alzheimer’s disease. Since mitochondrial disorders precede the formation of Aβ plaques, protecting mitochondrial tissue against oxidative stress is of great significance in the prevention and early treatment of Alzheimer’s disease.

Recently, Hyeon’s group successfully fabricated triphenylphosphine (TPP) functionalized CeO₂ nanoparticles for Alzheimer’s disease treatment (Figure 8A to C). As a SOD mimic, CeO₂ nanoparticles with high enzymatic activities can be used to reduce the level of overexpressed ROS in cells. Due to the mitochondrial targeting function of TPP, the functionalized nanoparticles can effectively localize to mitochondrial sites. In vivo results showed that the nanoparticles effectively alleviated the proliferation of reactive glial cells in an Alzheimer’s disease mice model and inhibited the neuronal death at the same time. In addition, Qu’s group designed a bifunctional system for Alzheimer’s disease therapy based on H₂O₂ response system, in which the antiaggregation performance of metal chelating agents and the antioxidant performance of CeO₂ nanoparticles were combined. The advantages of bifunctional system, such as admirable biocompatibility, good cellular uptake characteristics, and efficient release of metal chelating agents made it applicable in biomedicine. In vivo results demonstrated that the bifunctional system effectively inhibited the formation of Aβ aggregation, and reduced cellular ROS, thereby protecting cells from Aβ-related toxicity. In addition to CeO₂ nanozymes, Fe₃O₄ nanozymes were also able to be applied in treating Alzheimer’s disease. Fe₃O₄ nanoparticles mainly show peroxidase-like activity under acidic conditions, while they have CAT-like ability under neutral conditions.
Taking advantage of the CAT-like activity, Fan and coworkers have found that Fe$_3$O$_4$ nanozymes have a superb antioxidant capacity, which can effectively reduce the level of intracellular overexpressed ROS and protect cells from oxidative stress. In vivo results exhibited that the daily ingestion of Fe$_3$O$_4$ nanozymes effectively alleviated the neurodegeneration in an Alzheimer’s disease Drosophila model.

5.2 Nanozymes for Parkinson’s disease treatment

Similar to Alzheimer’s disease, Parkinson’s disease is a common neurodegenerative disease that usually occurs in the elderly. The most important pathological change of Parkinson’s disease is the degeneration and death of dopaminergic neurons in the substantia nigra of the mid-brain, resulting in a significant decrease in dopamine content in the striatum. Protecting nerves by scavenging ROS with nanozymes is of great benefit to the treatment of Parkinson’s disease.

Mugesh’s recent research reported that Mn$_3$O$_4$ nanozymes with nanoflower morphology could simultaneously exhibit SOD-, CAT-, and GPx-like activities, and the properties of which were related to the material morphology and size. In vivo results showed that the redox regulation of the nanozymes effectively protected Parkinson’s disease analogous cell model (SHSY–5Y) against the cytotoxicity induced by 1-methyl-4-phenylpyridinium (MPP$^+$). Therefore, the Mn$_3$O$_4$ nanozymes can be used as a potential therapeutic agent for neurodegenerative diseases caused by oxidative stress. Besides, Hyeon and coworkers developed a technology of scavenging ROS based on cellular localization to gain an in-depth insight on the pathological effects of ROS. They demonstrated the use of three different types of CeO$_2$ nanoparticles to selectively remove mitochondrial, intracellular, and extracellular ROS, and their application in the treatment of Parkinson’s disease. In vivo and in vitro results indicated that the removal of intracellular or mitochondrial ROS effectively inhibited microglia activation and lipid peroxidation, while the tyrosine hydroxylase in striatum of the Parkinson’s disease mice model was protected. The above results demonstrated that the reduction of intracellular and/or mitochondrial oxidative stress was the key to the treatment of Parkinson’s disease, while extracellular ROS was not an effective therapeutic target for the prevention of neurodegeneration.

In brief, a large amount of nanozymes with inherent antioxidant enzyme–mimicking properties have been developed for neuroprotection. These studies based on various nanozymes particularly contribute to the development of clinical applications of nanozymes in the treatment of neurodegenerative diseases.

6 FOR OTHER APPLICATIONS

Several studies have showed that nanozymes could be also used in other catalytic therapies. For instance, Shi and coworkers developed bioinspired melanin nanoparticles (MeNPs) with an admirable ability for scavenging excessive reactive oxygen and nitrogen species to protect brain from injury in ischemic stroke. Besides, Xue and coworkers designed a cascade catalyst by the integration of heme and GOD on graphene for the biomimetic production of antithrombotic species. Furthermore, Shimizu and coworkers reported that aging-related skin diseases induced by oxidative damage were treated by Pd and Pt (Pd@Pt) nanoparticles according to the SOD- and CAT-like activities. By combining uricase with Pt nanoparticles, Qu and coworkers formed a tandem catalytic system, in which uricase catalyzed a high uric acid to produce H$_2$O$_2$, that was further decomposed by Pt nanoparticles. The tandem catalytic system was applied for the treatment of hyperuricemia. In addition, Wang and coworkers designed a nanoparticle-based artificial RNA silencing machinery for the treatment of hepatitis C virus (HCV) through efficiently cleaving HCV RNA in the sequence specific manner. Recently, Wei and coworkers reported that Oltipraz-loaded poly (lactic-co-glycolic acid) nanoparticles with SOD-like activity were used in the treatment of acute kidney injury and renal fibrosis. All above, with the in-depth comprehension of nanozymes, the emerging artificial enzymes will be used in more fields.

7 CONCLUSION AND PERSPECTIVE

In summary, the emergence of nanozymes has broadened people’s understanding of mimic enzymes, making the study of mimic enzymes no longer limited to the design and synthesis of small organic molecules. Due to the excellent catalytic activity, nanozymes have shown great application prospects in numerous fields such as biosensing, environmental treatment, and disease treatment. However, compared with natural enzymes, the catalytic efficiency of nanozymes is far from the level of natural enzymes and the substrate selectivity is also poor. And up to now, there has been no mature nanozyme-based technology or product that has been truly applied to the clinic or the market. The main reasons are as follows:

1. It is impossible to precisely control the activity or efficiency of nanozymes. Although nanozymes are stable, their catalytic efficiency and selectivity in vivo are
difficult to control. It is necessary to develop new technologies and methods that can accurately control the behavior of nanozymes in vivo.

2. There are biosafety problems in nanozyme systems. The metabolic behavior and immunogenicity of nanozymes have not been fully studied, especially in animal experiments. At present, many similar catalytic systems are only tested in mice model, and more animal models or even clinical tests need to be further carried out.

3. There is no industrial standard for the application of nanozymes. There is a lack of clear criteria for material properties, especially for catalytic performance requirements such as how much catalytic efficiency is required to be usable for in vivo therapy. Therefore, relevant standardized indicators need to be further clarified and formulated to guide the application of nanozymes in different fields.

We believe that these unsolved issues will become the next frontier in the research of nanozymes, and accelerate the development of basic research and practical applications of nanozymes in catalytic therapeutics.

ACKNOWLEDGMENTS
This work was supported by National Key R&D Program of China (Grant Nos. 2020YFA0908500 and 2018YFA0901600), the National Natural Science Foundation of China (22001054), the Medical and Health Research Project of Zhejiang Province (2020KY239), the Hangzhou Overseas High-level Talent (Teams) Innovation and Entrepreneurship Program (4095C5062000604).

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ORCID
Hongcheng Sun https://orcid.org/0000-0003-0943-991X
Junqiu Liu https://orcid.org/0000-0003-1608-7908

REFERENCES
1. K. Chattopadhyay, S. Mazumdar, Biochemistry 2000, 39, 263.
2. G. D. DePillis, H. Wariishi, M. H. Gold, P. R. Ortiz de Montellano, Arch. Biochem. Biophys. 1990, 280, 217.
3. I. E. Holzbaur, A. M. English, A. A. Ismail, Biochemistry 1996, 35, 5488.
4. Y. Murakami, J. K. Ji, Y. Hisaeda, O. Hayashida, Chem. Rev. 1996, 96, 721.
5. R. Breslow, Acc. Chem. Res. 1995, 28, 146.
6. F. O. Caballero, C. Rousseau, B. Christensen, T. E. Petersen, M. Bols, J. Am. Chem. Soc. 2005, 127, 3238.
7. F. O. Caballero, J. Bjerre, L. Laustsen, M. Bols, J. Org. Chem. 2005, 70, 7217.
8. Y. Liu, B. Li, L. Li, H. Y. Zhang, Helv. Chim. Acta 2002, 85, 9.
9. H. Brunner, S. Altman, Chem. Ber. 1994, 127, 2285.
10. J. W. J. Knappen, A. W. van der Made, J. C. de Wilde, P. W. N. M. van Leeuwen, P. Wijkens, D. M. Grove, G. van Koten, Nature 1994, 372, 659.
11. P. Bhyrappa, J. K. Young, J. S. Moore, K. S. Suslick, J. Am. Chem. Soc. 1996, 118, 5708.
12. H. Zou, H. Sun, L. Wang, L. Zhao, J. Li, Z. Dong, Q. Luo, J. Xu, J. Liu, Soft Matter 2016, 12, 1192.
13. Y. Yin, S. Jiao, C. Lang, J. Liu, Soft Matter 2014, 10, 3374.
14. J. Li, Z. Wang, J. Zhou, M. Li, Q. Luo, Z. Dong, S. Shi, J. Liu, Colloids Surf. A 2018, 558, 95.
15. L. Z. Gao, J. Zhuang, L. Nie, J. B. Zhang, Y. Zhang, N. Gu, T. H. Wang, J. Feng, D. L. Yang, S. Perrett, X. Y. Yan, Nat. Nanotechnol. 2007, 2, 577.
16. X. Y. Yan, Prog. Biochem. Biophys. 2018, 45, 101.
17. M. Bassetti, M. Merelli, C. Temperoni, A. Astilean, Ann. Clin. Microbiol. Antim. 2013, 12, 22.
18. Q. Bu, B. Wang, J. Huang, S. Deng, G. Yu, J. Hazard Mater. 2013, 262, 189.
19. H. Sun, N. Gao, K. Dong, J. Ren, X. Qu, ACS Nano. 2014, 8, 6202.
20. Z. Wang, K. Dong, Z. Liu, Y. Zhang, Z. Chen, H. Sun, J. Ren, X. Qu, Biomaterials 2017, 113, 145.
21. W. Yin, J. Yu, F. Lv, L. Yan, L. R. Zheng, Z. Gu, Y. Zhao, ACS Nano. 2016, 10, 11000.
22. W. Y. Pan, C. C. Huang, T. T. Lin, H. Yi Hu, W. C. Lin, M. J. Li, H. W. Sung, Nanomedicine 2016, 12, 431.
23. L. Hall-Stoodley, J. W. Costerton, P. Stoodley, Nat. Rev. Microbiol. 2004, 2, 95.
24. H. C. Flemming, J. Wingender, Nat. Rev. Microbiol. 2010, 8, 623.
25. L. Gao, K. M. Giglio, J. L. Nelson, H. Sondermann, A. J. Travis, Nanoscale 2014, 6, 2588.
26. Z. Chen, H. Ji, C. Liu, W. Bing, Z. Wang, X. Qu, Angew Chem. Int. Ed. 2016, 55, 10732.
27. M. F. Huo, L. Y. Wang, Y. Chen, J. L. Shi, Nat. Commun. 2017, 8, 357.
28. X. Lu, S. Gao, H. Lin, L. Yu, Y. Han, P. Zhu, W. Bao, H. Yao, Y. Chen, J. Shi, Adv. Mater. 2020, 32, 2002246.
29. B. Yang, L. Ding, H. Yao, Y Chen, J. Shi, Adv. Mater. 2020, 32, 1907152.
30. X. Yi, L. Chen, X. Zhong, R. Gao, Y. Qian, F. Wu, G. Song, Z. Chai, Z. Liu, K. Yang, Nano. Res. 2016, 9, 3267.
31. J. Kim, H. R. Cho, H. Jeon, D. Kim, C. Song, N. Lee, S. H. Choi, T. Hyeon, J. Am. Chem. Soc. 2017, 139, 10992.
32. F. Balkwill, K. A. Charles, A. Mantovani, Cancer Cell 2005, 7, 211.
33. K. Aksu, A. Donmez, G. Keser, Curr. Pharm. Des. 2012, 18, 1478.
34. J. Wu, Y. Yu, Y. Cheng, C. Cheng, Y. Zhang, B. Jiang, X. Zhao, L. Miao, H. Wei, Angew. Chem. Int. Ed. 2020, 59, 2.
35. W. L. Wan, Y. J. Lin, H. L. Chen, C. C. Huang, P. C. Shih, Y. R. Bow, W. T. Chia, H. W. Sung, J. Am. Chem. Soc. 2017, 139, 12923.
36. J. M. Mc Ardell, J. Fridovich, J. Biol. Chem. 1969, 244, 6049.
37. H. Aebi, Method Enzymol. 1984, 105, 121.
38. J. T. Rotruck, A. L. Pope, H. E. Ganther, A. B. Swanson, D. G. Hafeman, W. G. Hokestra, Science 1973, 179, 588.
39. I. B. Haberle, L. Benov, I. Spasojevic, J. Fridovich, J. Biol. Chem. 1998, 273, 24521.
40. Y. Liu, Y. Cheng, H. Zhang, M. Zhou, Y. Yu, S. Lin, B. Jiang, X. Zhao, L. Miao, C. W. Wei, Q. Liu, Y. W. Lin, Y. Du, C. J. Butch, H. Wei, Sci. Adv. 2020, 6, eabb2695.
41. Y. Huang, Z. Liu, C. Liu, E. Ju, Y. Zhang, J. Ren, X. Qu, Angew. Chem. Int. Ed. 2016, 55, 6646.
42. W. Zhang, S. Hu, J. Yin, W. He, W. Lu, M. Ma, N. Gu, Y. Zhang, J. Am. Chem. Soc. 2016, 138, 5860.
Hongcheng Sun received his B. Sc degree (2011) in Polymer Materials and Engineering from Jilin University. In 2016, he obtained his Ph. D in Polymer Chemistry and Materials from the same University under the supervision of Dr. Junqiu Liu. Subsequently, he gained postdoctoral training in Washington University in St. Louis (WUSTL), U.S.A. He became an associate professor in 2019 at the College of Material, Chemistry and Chemical Engineering in Hangzhou Normal University (HZNU). His research interests are focused on the investigation of nano/biology interfaces for advanced construction of functional biomaterials, as well as MOF hybrids for biological applications.

Junqiu Liu received his PhD from the State Key Laboratory of Supramolecular Structure and Materials, College of Chemistry, Jilin University in 1999 under the supervision of Professor Jiacong Shen. Following his doctoral studies, he was a Humboldt Fellow and a Postdoctoral Fellow with Professor Gunter Wulff at the Institute of Organic and Macromolecular Chemistry, Heinrich-Heine University, Germany. Subsequently, he joined the faculty in Jilin University as a full professor in 2003. He is currently a full professor in College of Material, Chemistry and Chemical Engineering from Hangzhou Normal University (HZNU). His main research interests include biomimetic systems, enzyme design and bio-supramolecular self-assembly.

How to cite this article: S. Liu, J. Xu, Y. Xing, T. Yan, S. Yu, H. Sun, J. Liu, VIEW 2022, 3, 20200147. https://doi.org/10.1002/VIW.20200147

**AUTHOR BIOGRAPHIES**

**Shengda Liu** received his PhD from the State Key Laboratory of Supramolecular Structure and Materials, College of Chemistry, Jilin University under the supervision of Professor Junqiu Liu, in 2020. Currently, he is a postdoctoral fellow of Hangzhou Normal University (HZNU) and Central South University (CSU). His research is mainly on signal transduction, ion transport and bio-catalysis.