REVIEW

The age of bioinspired molybdenum-involved nanozymes: Synthesis, catalytic mechanisms, and biomedical applications

Yan Zu1 | Huiqin Yao2 | Yifan Wang2 | Liang Yan1 | Zhanjun Gu1 | Chunying Chen1 | Lizeng Gao3 | Wenyan Yin1

1 CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, Institute of High Energy Physics and National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing, China
2 School of Basic Medicine, Ningxia Medical University, Yinchuan, China
3 Key Laboratory of Protein and Peptide Pharmaceuticals, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

Correspondence
Wenyan Yin, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, Institute of High Energy Physics and National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing 100049, China.
Email: yinwy@ihep.ac.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 51772293, U1932112; CAS Key Laboratory of Nano-BioInterface, Grant/Award Number: 20NB101; Natural Science Foundation of Beijing Municipality, Grant/Award Number: 2202084; Natural Science Foundation of Ningxia Province, Grant/Award Number: 2020AAC0315; National Basic Research Programs of China; Scientific Research Project of the Ningxia Higher Education Institutions of China

Abstract
Molybdenum (Mo), as a nontoxic and low-cost transition metal, has been employed for synthesis of various Mo-based nanomaterials with unique structures and physicochemical features to achieve various properties. Especially, bioinspired Mo-based nanomaterials show great potential for the construction of novel nanozyme catalysts due to their variable oxidation states. Overcoming drawbacks of natural enzymes, bioinspired Mo-based nanozymes not only provide effective catalytic sites or multivalent elements to mimic natural enzymes, but also present multiple functions for interfacing with various biomicroenvironments. Construction of vast Mo-based nanozymes has attracted enormous interest in biomedicine. Exogenous/endogenous stimuli enable the user to tailor the catalytic activities of Mo-based nanozymes. Additionally, tunable physicochemical properties also have a significant influence on their enzyme-like activity. In this review, we comprehensively summarize typical synthesis strategies, catalytic mechanism, and types of enzyme-like activity of the bioinspired Mo-based nanozymes. We mainly highlight desired merits of bioinspired Mo-based nanozymes related to tunable enzyme-like activity, stability, and multifunctionality through regulating their physicochemical properties. Furthermore, we intend to discuss their biomedical applications in biosensing and detection, oncotherapy, and combating bacteria. Finally, current challenges and future perspectives of the Mo-based nanozymes are also proposed.

KEYWORDS
biomedical applications, catalytic mechanisms, molybdenum, nanozyme, physicochemical properties

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. VIEW published by Shanghai Fuji Technology Consulting Co., Ltd, authorized by Professional Community of Experimental Medicine, National Association of Health Industry and Enterprise Management (PCEM) and John Wiley & Sons Australia, Ltd.

https://doi.org/10.1002/VIW.20200188
As typical transition-metal-based nanomaterials, molybdenum (Mo)-based nanomaterials have multiphases and polyvalences. The variable oxidation states can be attributed to the existence of many easily lost single electrons in their electronic configuration. The main valence states of Mo elements include Mo (0), Mo (III), Mo (IV), Mo (V), and Mo (VI). Importantly, Mo-based compounds can be converted between variable valence states, making them promising candidates for catalysts. Besides the function of catalysts, Mo-based nanomaterials have distinct physicochemical properties such as large surface area, easy surface modification, and good near-infrared (NIR) photothermal conversion efficiency, making them have broad applications in electronics, energy, sensing as well as biomedicine. For biomedicine, Mo, an essential trace element and nutrient that is necessary for the survival of all living body from bacteria, plants, to humans, serves as a cofactor for various Mo-based enzymes such as xanthine dehydrogenase, aldehyde oxidase, sulfite oxidase (SuOx), and nitrate reductase (NRase). The presence of Mo in biological systems as key component of natural enzymes catalyzing redox and oxygen transfer reactions is well established. For example, nitrogen fixation in biological system can be catalyzed by NRase, an enzyme complex containing an iron–Mo cofactor (FeMo). However, just like any other natural enzymes, Mo-based enzymes are proteins, which are often unstable in storage, expensive to manufacture as well as sensitive to harsh physicochemical conditions.

Nanomaterials are promising substitutes for traditional enzymes with novel physicochemical properties and intrinsic enzyme-like catalytic activity. With the rapid development of nanotechnology, biomedical applications of nanomaterials have become an intensive research focus. Compared to natural enzymes, nanomaterials with robust catalytic activity, low cost, high stability, and easy large-scale production can catalyze the reaction of substrates even under harsh physiological conditions. By combining superior physicochemical properties with enzyme-like catalytic activity, nanomaterials can offer multifunctional bioapplications from detection to monitoring and therapy. Since the discovery of Fe3O4 nanoparticles (NPs) with inherent peroxidase (POD) activity by Yan et al., worldwide scholars have successively revealed the enzymatic-like properties of various nanomaterials to mimic the structures and functions of natural enzymes. The enzyme-mimicking nanomaterials include noble metals, transition metals oxides/sulfides, carbon-based nanomaterials (e.g., graphene oxide [GO], carbon nanotubes, and carbon quantum dots [QDs]), and so on, which have been widely applied in various fields. However, not all nanomaterials are suitable for biological systems concerning the problem of biosafety. As a state-of-the-art artificial enzyme, bioinspired Mo-based nanomaterials have tunable enzyme-like activity, high stability, and versatile functions. Based on these advantages, they can be utilized for biodetection, antioxidant, and disease therapy. Meanwhile, Mo-based nanomaterials have also improved biosafety and biodegradability by tuning their physicochemical properties. For instance, exfoliated MoS2 nanosheets (NSs) have lower cytotoxicity than graphene and its analogues. Decoration with Fe3O4 NPs greatly facilitates high stability of MoS2 nanoflakes (NFs) in a physiological environment. MoO2, NSs and NPs with high enzyme-like activity functionalized with polyethylene glycol (PEG) showed high stability in acidic microenvironments and rapid degradation and excretion at physiological pH value in vivo. The permissible amount of Mo in circulation is 2 mg/day and complexes of Mo also showed an antidiabetic activity. In consideration of their safety in biomedical applications, bioinspired Mo-based nanomaterials have great development prospects in future. More importantly, due to the remarkable catalytic function for specific biochemical reactions, Mo-based nanomaterials have also been developed as promising nanomaterials whose catalytic activity can be tailored by exogenous/endogenous stimuli or physicochemical properties.

The classes of bioinspired Mo-based nanomaterials so far include molybdenum disulfide (MoS2), molybdenum selenide (MoSe2), molybdenum oxide (MoOx), molybdenum carbide (Mo2C), and hybrid Mo-based nanomaterials (TiO2@MoS2/CoFe2O4, Au–Pd/MoS2, MoS2/GO, MoS2:CeO2, etc.). Hybrid Mo-based nanomaterials can integrate new functional components into their hybrid structures, and each form has its own exceptional properties. MoS2 and MoSe2 are typical members of two-dimensional (2D) graphene-like transition metal dichalcogenides (TMDCs), and each form has its own exceptional properties. Strategies for synthesis of Mo-based nanomaterials include exfoliation, hydrothermal/solvothermal synthesis, thermal decomposition, and pulsed laser ablation. These strategies can control the physicochemical properties of nanomaterials such as phase structure, morphology, surface modification, and size, consequently affecting their enzyme-like activities. In 2014, the MoOx NPs were first reported to have oxidase (OXD)-like catalytic activity and the MoS2 NSs were almost simultaneously reported to have intrinsic POD-like catalytic activity. MoSe2 and hybrid Mo-based nanomaterials were then found to possess various enzyme-like activities, including POD, OXD, catalase (CAT), superoxide dismutase (SOD), and NRase.
To date, a number of reviews have provided an overview of nanozymes for various applications. However, a comprehensive summary of bioinspired Mo-based nanozymes in the area of biomedical applications has yet to appear. In this review, to highlight the importance of Mo-based nanozymes in the multi-interdisciplinary fields of chemistry, biology, and medicine, we systematically summarize the recent progress on the design of bioinspired Mo-based nanozymes and how physicochemical effects are related to enzyme-like biocatalytic activity and the catalytic mechanisms (Figure 1). We further discuss design strategies to exploit the relationship between physicochemical properties and the enzyme-like catalytic activity, consequently presenting the advances of Mo-based nanozymes in biomedicine for biosensing and detection, cancer therapy, and combating bacteria. Finally, current challenges and future perspectives of the bioinspired Mo-based nanozymes will be highlighted. Although the current developments are in infancy, by entering the age of Mo-based nanozymes, they are expected to have more wide biomedical applications in preclinical and clinical phases.

2 SYNTHESIS OF MO-BASED NANOZYMES

Nanozymes, as new alternatives to natural enzymes, have gained improved catalytic performance through regulating their physicochemical properties. Synthesis of nanozymes is the precondition for investigation of their properties and applications. Although much progress in nanozyme studies has been made, it is found that their catalytic activities are lower than those of natural enzymes, which is mainly attributed to the low density of active sites and low electron mobility on nanozyme surfaces. Mo-based nanozymes have variable phase structures and oxidation states, including Mo (0), Mo (III), Mo (IV), Mo (V), and Mo (VI). Far easier loss of single electrons in their electronic configuration is the main reason for their variable oxidation states. Tailored synthetic strategies can control the phase structure, oxidation states, and morphology of nanozymes, consequently influencing their enzyme-like catalytic behaviors such as substrate selectivity and multienzyme mimetic activity. Therefore, the ingenious synthesis and rational design of highly efficient Mo-based nanozymes are very important. In this section, we will introduce the main strategies for the synthesis of various Mo-based nanozymes.

To date, Mo-based nanozymes have been synthesized with different compositions and phases, including MoX2 (X = S, Se), MoOx (2 ≤ x ≤ 3), Mo2C as well as their hybrids. Mo-based nanozymes with diverse morphologies such as NSs, NFs, NPs, and QDs have also been fabricated. It is worth noting that surface modification of Mo-based nanozymes is often utilized to regulate their physicochemical properties such as size, surface charge, morphology,
and composition. In addition, different surface modifications can affect the enzyme-like catalytic activity of Mo-based nanozymes and make them highly stable and well biocompatible. A number of bottom-up and top-down approaches including exfoliation (e.g., liquid exfoliation, ultrasonic exfoliation, and chemical exfoliation), hydrothermal/solvothermal synthesis, thermal decomposition as well as pulsed laser ablation can be used to synthesize Mo-based nanozymes (Table 1).

Herein, representative methods for synthesis of Mo-based nanozymes are presented. Multiple MoS$_2$ NSs with a few layers can be extensively produced by exfoliation of bulk MoS$_2$. MoS$_2$ NFs with an average size of 390 nm can be prepared via a simple, one-step hydrothermal method. MoSe$_2$ NFs can be prepared by liquid ultrasonic exfoliation method in a mixture of water and alcohol. MoO$_3$ nanodots can be fabricated via pulsed laser ablation method in MoS$_2$ NSs solutions. In addition, multifunctional hybrid Mo-based nanozymes can also be fabricated. For instance, ternary TiO$_2$@MoS$_2$/CoFe$_2$O$_4$ composite nanofibers with superior POD-like properties have been constructed via a two-step hydrothermal process. The MoS$_2$ NSs were first grown on TiO$_2$ nanofibers to act as an interfacial barrier to load ultrafine CoFe$_2$O$_4$ NPs. Zhang et al. reported that the Pt–MoO$_3$ hybrid nanomaterials with enhanced POD-like catalytic activity were obtained via a wet-chemical synthesis method after growth of Pt NPs on several-layered MoO$_3$ NSs. Among these synthetic methods, both hydrothermal method and liquid exfoliation strategies have distinct advantages for efficiently preparing Mo-based nanozymes with large-scale, controllable size, and facile modification. In particular, liquid exfoliation strategies using surfactants, polymer solutions as well as organic solvents can not only weaken the interlayer interactions in Mo-based nanozymes for effective exfoliation but also avoid the use of explosive n-butyllithium for intercalation, which is difficult to be handled and readily introduces impurities. Both of the hydrothermal method and liquid exfoliation strategies are beneficial for modulating the physiochemical properties such as phase structure and surface defects that could affect catalytic activity.

There are two important factors for improving the enzyme-like catalytic performance of Mo-based nanozymes: (i) more active sites or active centers and (ii) higher conductivity. The abundant defects exposed on the surface of Mo-based nanozymes favor the generation of active sites. Up to now, much effort has been focused on the synthesis of Mo-based nanozymes with defect structures or doped elements (N, Pt, Li, etc.) to generate more active edge sites exposure for further improving the catalytic activity. The abundant defects exposed on the surface of Mo-based nanozymes favor the generation of active sites. Up to now, much effort has been focused on the synthesis of Mo-based nanozymes with defect structures or doped elements (N, Pt, Li, etc.) to generate more active edge sites exposure for further improving the catalytic activity. It was also reported that the thinner MoS$_2$/GO composites with better conductivity had higher catalytic activity than that of thicker one. The employment of proper synthetic strategies is the main factor in the low-cost synthesis of nanozymes.

### Table 1: Typical synthesis methods for Mo-based nanozymes

| Nanozymes | Synthesis methods     | Morphology          | Rang of size                  | Reference |
|-----------|-----------------------|---------------------|-------------------------------|-----------|
| MoO$_x$   | Exfoliation           | Sheet-like          | 3–12 nm (thickness)           | 48,69     |
|           | Hydrothermal          | Spherical           | 3.42 nm; 5–14 nm               | 79,146    |
|           | Hydrothermal          | Rice-like           | 10–50 nm                      | 31        |
|           | Pulsed laser ablation | Spherical           | 3–5 nm                        | 41        |
|           | Solvothermal reaction | Nanourchin          | 142.8 nm                      | 39        |
| MoS$_2$   | Exfoliation           | Spherical           | 30–50 nm; 2–3 nm; 3.7 nm       | 56,139,147|
|           | Hydrothermal          | Sheet-like          | 1–5 nm (thickness)             | 43,99     |
|           | Hydrothermal          | Sheet-like          | ∼300 nm (lateral); 100–150 nm (thickness) | 34,148   |
|           | Hydrothermal          | Nanotube-like       | 350 nm (diameter), 1–3 μm (length) | 92        |
|           | Hydrothermal          | Nanoribbon          | 150–700 nm                    | 72        |
|           | Hydrothermal          | Flower-like         | 25 nm; 150 nm                 | 27,149    |
|           | Hydrothermal          | Spherical           | 2–4 nm; ∼1.8 nm               | 93,150    |
|           | Hydrothermal          | Spherical           | 5 nm; 70 nm                   | 51,97     |
|           | Laser ablation        | Spherical           | 10–80 nm                      | 86        |
|           | Morrison              | Sheet-like          | 1.5–2 nm (thickness)           | 151       |
|           | Thermal decomposition | Spherical           | 1.3 nm                        | 95        |
| MoSe$_2$  | Exfoliation           | Sheet-like          | Few-layered; one single layer  | 30,116    |
with high yield and high catalytic activity, which is a significant advantage when compared with nature enzymes. Moreover, although systematically comparing the activities of Mo-based nanozymes synthesized by different methods is rare, use of the concept of specific activity for enzymology to evaluate the activity normalized as unit activity/mass of nanozymes may be feasible. Specifically, the amount of nanozyme that catalyzes 1 μmol of product per minute was used to define one nanozyme activity unit. Overall, the synthetic methodology can influence the physicochemical properties of Mo-based nanozymes, consequently resulting in different catalytic activities.

3 | TYPES AND MECHANISMS OF ENZYMATIC ACTIVITY OF MO-BASED NANOZYMES

Using Mo-based nanomaterials to mimic the catalytic function of natural enzymes is an interesting yet challenging task. Currently, Mo-based nanomaterials have been reported to mimic several enzymatic activities such as POD, OXD, CAT, SOD, and NRase. We discuss here the enzymatic activities and catalytic mechanisms of Mo-based nanozymes.

3.1 | Mo-based nanozymes with POD-like activity

PODs especially horseradish peroxidase (HRP) can catalyze peroxides such as H₂O₂ to form reactive oxygen species (ROS) (e.g., hydroxyl radicals [•OH]) and water. In general, POD-like nanozymes have two catalytic pathways including ROS production and electron transfer. Most Mo-based nanozymes as prototypical TMDCs possess intrinsic POD-like activity. Various reports have demonstrated that Mo-based nanozymes as POD mimics can catalyze oxidation of diverse chromogenic substrates, such as colorless 3,3′,5,5′-tetramethylbenzidine (TMB), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), o-phenylenediamine (OPD), 3,3′-diaminobenzidine, and dopamine into colored oxides. For example, colorless TMB can be oxidized by Mo-based nanozymes into blue oxide of TMB (oxTMB) in the presence of H₂O₂ (Figure 2A).

Similar to nature enzymes, the catalytic activity of Mo-based nanozymes is affected by reaction conditions, such as pH value, concentration of substrates, temperature, and reaction time. Most Mo-based nanozymes have high catalytic activity at the temperature of 25–40 °C and the pH of 3.5–6.0. Their POD mimetic activity follows typical Michaelis–Menten kinetics and ping-pong catalytic mechanism, similar to natural HRP. In addition, the important kinetic parameters such as Michaelis–Menten constant (Kₘ) and maximum reaction velocity (Vₘₓ) have been used to evaluate catalytic efficiency of the POD-like Mo-based nanozymes. A lower Kₘ value implies greater affinity of the enzyme toward the substrate.

The POD-like catalytic activity of MoS₂ NSs was first reported in 2014. The MoS₂ NSs can catalytically oxidize TMB by H₂O₂ to produce blue oxTMB. The catalytic activity followed the typical Michaelis–Menten kinetics and depended on temperature, pH, H₂O₂ concentration, and reaction time. The high catalytic activity over a wide pH range (2.0–7.5) of MoS₂ NSs was applied to detect glucose in serum samples. Since then, many MoS₂ nanozymes with different surface coatings, hybridization, and heteroatom doping have been reported to possess POD-like catalytic activity. Based on the previous study, charge transfer from TMB to MoS₂ NSs is closely related to the p-type nature of few-layered MoS₂ NSs. The rich active sites located at the edges of MoS₂ NSs have been thought to facilitate the electron transfer between TMB and H₂O₂ during the catalytic reaction. In this process, TMB molecules are absorbed on the surfaces of MoS₂ NSs and promote lone-pair electrons from the amino groups of TMB to MoS₂ NSs, leading to an increase in electron density and mobility in the MoS₂ NSs surface. Thus, the electron transfer from MoS₂ NSs to H₂O₂ could be accelerated, causing H₂O₂ to be reduced to H₂O in acidic media and TMB to be oxidized by H₂O₂ with increased reaction rate. Moreover, MoS₂ NSs could also effectively catalyze the decomposition of H₂O₂ in acidic media into •OH than in the neutral medium. The catalytic mechanism is based on promoting electron transfer during the Fenton-like reaction to produce an intermediate •OH to oxidize the H₂O₂ (Figure 2B).

Apart from MoS₂ NSs, few-layered MoSe₂ NSs also possess intrinsic POD-like activity. The apparent Kₘ values of MoSe₂ NSs toward TMB and H₂O₂ as substrates were 30 and 22.8 times lower, respectively, than those of HRP, which indicates that the MoSe₂ NSs had a higher affinity for both TMB and H₂O₂ substrates than HRP. In the catalytic reaction, the electron-rich MoSe₂ NSs transfer their electrons to nearby H₂O₂. Subsequently, the decreased electron concentration of the MoSe₂ NSs promoted the electron transfer from TMB to the MoSe₂ NSs. As a result, TMB was oxidized to blue oxTMB and H₂O₂ was reduced to H₂O, similar to other nanozymes like GO and Co₃O₄ NPs. Moreover, compared to Mo₂S and MoSe₂, MoO₂ has more oxygen vacancies. Thus, development of MoO₂ nanozymes is highly desired. Very recently, Guo et al. reported that MoO₂ NPs had POD-like activity and a higher affinity to H₂O₂ than MoSe₂ NSs. The ping-pong catalytic mechanism of MoO₂ NPs was similar to HRP. They also demonstrated that MoO₂ NPs can
facilitate the electron transfer between $\text{H}_2\text{O}_2$ and TMB and then accelerate the decomposition of $\text{H}_2\text{O}_2$. These MoO$_2$ NPs can be used for colorimetric assay of acetylcholinesterase inhibitor, an important basis for the treatment of Alzheimer’s disease. MoO$_2$ with different morphologies such as nanorods, nanowires, and hybrid structures also have different POD-like activity for biomedical applications.\textsuperscript{58,80,81}

Single-atom (SA) nanozymes with isolated active metal centers anchored on solid supports have recently presented new breakthroughs in biocatalysis. The unique structure and coordination environment are in favor of their catalytic active sites at an atomic scale. For instance, SA Mo-based nanozyme has been constructed to possess intrinsic POD-like catalytic activity that was confirmed by experimental and theoretical studies.\textsuperscript{82} In virtue of the
different adsorption energies of MoS2 substrate on different parts of the SA Co–MoS2, SA Co can act as an electron transfer mediator, whereas the POD-like property of the MoS2 support may result from the occurrence of Fenton-like reaction because the support was likely to attract TMB. This study paves the way for in-depth investigation of single-atom catalyst as well as providing inspiration for designing hybrid nanozymes. Very recently, Cui et al. also reported a series of heterogeneous Mo SA nanozymes (named as MoSA–N3–C). They found that the POD-like specificity was well regulated by the coordination numbers of single Mo sites. The MoSA–N3–C catalyst showed exclusive POD-like behavior via a homolytic pathway, whereas MoSA–N2–C and MoSA–N4–C catalysts had different heterolytic pathway. The geometrical structure differences and orientation relationships of the frontier molecular orbitals toward these MoSA–N3–C POD mimics can account for the mechanism of this coordination number–dependent enzymatic specificity.83 In short, SA nanozymes possess excellent catalytic activity and selectivity because of the homogeneity of their active sites and geometric structure, overcoming some limitations of other nanozymes.46 Hence, more superior SA Mo-based nanozymes are expected to be explored in the future.

3.2 | Mo-based nanozymes with OXD-like activity

Natural oxidases can catalyze the oxidation of substrates into an oxidized product by reaction with O2. The O2 molecule acts as an electron acceptor and can be reduced into H2O or H2O2 (or O2•− in some cases). The OXD-mimicking activity of Mo-based nanozymes has attracted great attention. In particular, sulfite oxidase (SuOx), a Mo-dependent enzyme localizing to the intermembrane space of mitochondria, can catalyze the oxidation of sulfite (SO32−) to sulfate (SO42−) in the final degradation of sulfur-containing amino acids. Tremel et al. first reported that ultrasmall MoO3 NPs acted with high similarity with the structure of active site of natural SuOx enzyme to oxidize SO32− to SO42− under physiological conditions (Figure 3A).42 The surface of MoO3 NPs was decorated with dopamine to anchor triphenylphosphonium ions (TPP) to
form TPP-MoO$_3$ NPs for membrane crossing and mitochondrial targeting. Steady-state kinetics studies suggested that the active Mo$^{6+}$ of the nanozyme was firstly converted to Mo$^{4+}$ on account of sulfite oxidation, and then reverted to Mo$^{6+}$ by two-electron reduction reactions of ferricyanide. These TPP-MoO$_3$ NPs with good biocompatibility could specifically accumulate at mitochondria and promote the recovery of the SuOx activity of SuOx knockdown liver cells in vitro, enabling the TPP-MoO$_3$ NPs as a potential therapeutic agent for sulfite oxidase deficiency.

Similarly, PEGylated-MoO$_3$-$x$ (P-MoO$_3$-$x$) NPs, as another SuOx nanozyme, were also fabricated (Figure 3B).$^{79}$ Their SuOx-like activity was 12 times higher than that of bulk MoO$_3$. The enhanced enzyme mimetic activity of P-MoO$_3$-$x$ was ascribed to the abundant oxygen vacancies as catalytic hotspots, allowing effective SO$_3^{2-}$ capture ability. In this study, vitamin B1 can be irreversibly chelated by SO$_3^{2-}$ and has electrostatic interaction with P-MoO$_3$-$x$ NPs, consequently inhibiting the SuOx activity of P-MoO$_3$-$x$ NPs. Therefore, the SuOx-like P-MoO$_3$-$x$ NPs have been used to detect vitamin B1 with high sensitivity through a colorimetric method.

Inspired by the SuOx mimicking of MoO$_3$ NPs, Chen et al. recently demonstrated that MoO$_3$ NPs exhibit promising OXD-like activity.$^{84}$ These NPs can catalyze the oxidation of colorless ABTS to produce a green product. As a specific target molecule of $^{1}$O$_2$, 2,2,6,6-tetramethylpiperidine (TEMP) can be oxidized by $^{1}$O$_2$ to be tetramethylpiperidinolxoy (TEMPO). In this study, the electron spin resonance signals of TEMPO were observed in the MoO$_3$ NPs solution, demonstrating the production of $^{1}$O$_2$ during enzyme-like catalytic reaction. The dissolved $^{1}$O$_2$ was adsorbed onto the surface of MoO$_3$ NPs and then formed $^{1}$O$_2$, which finally oxidized ABTS.

Acid phosphatase (ACP) could catalyze the hydrolysis of the ascorbic acid 2-phosphate (AAP) substrate to generate ascorbic acid, which can fade the color from the MoO$_3$ NP-mediated ABTS oxidation. The MoO$_3$ NPs have been used as ACP detection by integrating the OXD-like property of the MoO$_3$ NPs with the ACP-catalyzed hydrolysis of AAP.

### 3.3 Mo-based nanozymes with CAT-like activity

CAT is a strong antioxidant enzyme. It can catalytically decompose H$_2$O$_2$ to O$_2$ and H$_2$O. Compared to POD-like activity, the CAT-like activity of Mo-based nanomaterials is rarely studied. Recently, Rezaeifard et al. exploited blackberry-shaped NPs composed of amorphous {Mo$_{72}$Fe$_{30}$} clusters, which showed CAT-like activity under visible-light irradiation.$^{85}$ The superior catalytic activity of {Mo$_{72}$Fe$_{30}$} was mainly attributed to its high surface area induced by its low crystallinity and easily formed blackberry structures that can enhance the adsorption of both H$_2$O$_2$ molecules and visible light. The {Mo$_{72}$Fe$_{30}$} nanoclusters preserved their integrity during H$_2$O$_2$ decomposition. According to the scavenging experiments, a nonradical mechanism was suggested for dismutation of H$_2$O$_2$ on the surface of the clusters. The catalyst preserved its catalytic efficiency and reproducible kinetic results were observed for O$_2$ generation during six runs. Moreover, the kinetic experiments showed that the decomposition of H$_2$O$_2$ followed first-order kinetics and the energy barrier for the O–O bond cleavage could be lowered by {Mo$_{72}$Fe$_{30}$} nanoclusters in the decomposition of H$_2$O$_2$. The high stability and efficient reusability make the {Mo$_{72}$Fe$_{30}$} nanzyme become a reliable catalyst for H$_2$O$_2$ decomposition.

### 3.4 Mo-based nanozymes with multienzyme-like activities

Inspired by cascaded reactions occurring in living organisms, researchers have attempted to design nanozymes with cascaded multiple-enzyme mimicking properties. Due to variable valence states of Mo elements, various kinds of Mo-based nanozymes can show multienzyme-like activities that are usually pH dependent, and the catalytic mechanism is similar to other nanozymes like Prussian blue nanozymes and cobalt oxide nanozymes (Figure 4).$^{18,41,43}$ Zheng et al. prepared Mo$_2$S$_2$ NSs using liquid exfoliation of pristine Mo$_2$S$_2$ powder in a mixed solution. The Mo$_2$S$_2$ NSs possess three mimicking enzymes activities including POD, CAT, and SOD under physiological conditions.$^{43}$ Moreover, the Mo$_2$S$_2$ NSs were utilized to establish an antioxidant system for cytoprotection, catalytically dismutating superoxide radical (O$_2^{•−}$) into H$_2$O$_2$ and then decomposing H$_2$O$_2$ into O$_2$ and water (Figures 5A and 5B). Interestingly, the Mo$_2$S$_2$ NSs can also efficiently eliminate other free radicals such as ‘OH, nitrogen-centered free radicals (‘DPPH), and nitric oxide (‘NO), showing their advantage in the modulation of oxidative stress. Furthermore, the Mo$_2$S$_2$ nanozymes can effectively protect cells from oxidative injury induced by H$_2$O$_2$.

Likewise, Wang and coworkers demonstrated that MoO$_{3−x}$ nanodots possess favorable CAT- and SOD-mimicking activities owing to the efficient charge transition of Mo$^{5+}$/Mo$^{6+}$ on the surface of nanodots. Particularly, MoO$_{3−x}$ nanodots exhibited high CAT-like catalytic activity at various pH values (3.0–9.0) and the optimum catalytic activity was observed in alkaline pH 9.0. The MoO$_{3−x}$ nanodots can be used as a multifunctional amyloid beta (Aβ) fibrillation modulator to alleviate Aβ-$
**FIGURE 4** Mechanism diagram of the multienzyme-like activities of Mo-based nanozymes

**FIGURE 5** Multienzyme-like activities of Mo-based nanozymes. (A) MoS$_2$ NSs with intrinsic activity of mimicking SOD, CAT, and POD under physiological conditions. (B) Nanozymatic antioxidant system (NAS) based on MoS$_2$ NSs catalyzing the dismutation of O$_2^•−$ into H$_2$O$_2$ and the subsequent decomposition of H$_2$O$_2$ into O$_2$ and water. Reproduced with permission. Copyright 2018, American Chemical Society. (C) Fullerene-like MoS$_2$ NPs as cascade catalysts improving lubricant and antioxidant abilities of artificial synovial fluid. (D) Artificial enzymatic cascade system based on fullerene-MoS$_2$ nanoparticles elimination of ‘OH by catalyzing the disproportionation of O$_2^•−$ to H$_2$O$_2$ and subsequent disproportionation of H$_2$O$_2$ into O$_2$. Reproduced with permission. Copyright 2019, American Chemical Society.
mediated oxidative stress, consequently relieving amyloid aggregation-induced neurotoxicity.\textsuperscript{41} Besides, Zheng and coworkers demonstrated that fullerene-like MoS\textsubscript{2} (F-MoS\textsubscript{2}) NPs possess intrinsic CAT- and SOD-like activities under physiological conditions.\textsuperscript{86} By integrating these unique properties, a self-organized cascade catalytic system was prepared, which resulted in the catalytic disproportionation of \( \text{O}_2^{-}\) into \( \text{H}_2\text{O}_2 \) and then the transformation of \( \text{H}_2\text{O}_2 \) into \( \text{O}_2 \) (Figures 5C and 5D). The F-MoS\textsubscript{2} NPs were utilized to prevent human umbilical vein endothelial cells from oxidative stress caused by high-level \( \text{H}_2\text{O}_2 \). Based on the cascade system, F-MoS\textsubscript{2} NPs were combined with hyaluronic acid (HA), regulating the excessive ROS and preventing the depolymerization of HA in artificial synovial fluid. These multiple enzyme-mimicking activities equipped Mo-based nanozymes for a variety of advanced bioapplications. Furthermore, such Mo-based nanozymes may reveal insights into the ultimate form of nanozymes. However, the mechanism of the multi-enzyme-mimicking nanozymes and the optimal physiological environment of enzyme-like activity of each type of these enzymes in one multi-enzyme-mimicking nanozyme need to be further investigated. Whether these multiple enzymatic activities will interfere with each other or not is still unclear.

3.5 Mo-based nanozymes with NRase-like activity

Nitrate anion (\( \text{NO}_3^- \)) is a simple, abundant, and relatively stable species, yet plays a significant role in global cycling of nitrogen, global climate change, and human health.\textsuperscript{87} In nature, the catalytic reaction of NRase at neutral pH value using a highly-conserved Mo center ligated mainly by oxo- and thiolate groups is the most effective strategy to realize nitrate reduction reaction. The reaction catalyzed by NRase is shown in Equation 1. All NRase are Mo-dependent enzymes. So far, only a few studies have reported that nanomaterials can mimic the activity of NRase. In 2008, a peptide-mediated synthesis of CdS–Pt NPs system was demonstrated as a robust inorganic mimic for the reduction of \( \text{NO}_3^- \) to \( \text{NO}_2^- \) with activity that outperforms NRase enzyme by more than 23-fold.\textsuperscript{88} Recently, Nakamura and coworkers reported that MoS\textsubscript{2} NSs can electrochemically catalyze the reduction of \( \text{NO}_3^- \)/\( \text{NO}_2^- \) to ammonia (\( \text{NH}_3 \)) over a wide pH range (pH 3–11).\textsuperscript{89} The pH dependence of the onset potential of the denitrification current showed that this superior activity was in virtue of the ability to cause concerted proton–electron transfer, resulting in a turnover frequency analogous to that of the extent Mo-dependent NRase. Similar to biological dissipatory denitrification, MoS\textsubscript{2} NSs catalyzed \( \text{NO}_3^- \) reduction to \( \text{NH}_3 \) through NO and \( \text{N}_2\text{O} \) intermediates, which was indicated by online differential electrochemical mass spectroscopy. These results demonstrated that the MoS\textsubscript{2} NSs function as a new family of bioinspired electrochemical denitrification catalysts.

\[
\text{NO}_3^- + 2\text{H}^+ + 2e^- \rightarrow \text{NO}_2^- + \text{H}_2\text{O} \quad (1)
\]

The same group also synthesized an oxo-MoS\textsubscript{x} catalyst that had a hierarchical structure of assembled NSs (Figure 6).\textsuperscript{44} The catalyst was capable of electrochemically reducing \( \text{NO}_3^- \) to \( \text{NO}_2^- \) and \( \text{NH}_4^+ \) under physiological pH conditions. In contrast, a commercial crystalline MoS\textsubscript{2} (c-MoS\textsubscript{2}) was utilized as a reference, which did not have oxo species. The results indicated barely any \( \text{NO}_2^- \) and \( \text{NH}_4^+ \) were produced when c-MoS\textsubscript{2} was applied as the electrocatalyst. The reduction of \( \text{NO}_3^- \) on the oxo-MoS\textsubscript{x} catalyst occurred at a redox-active, axially symmetric Mo\textsuperscript{V}(=O)S\textsubscript{4} intermediate, which represented the first oxo- and thiolate-ligated Mo at neutral pH that structurally resembled the active center of NRase. The identification and characterization of oxo- and thiolate-ligated Mo intermediates pave the way to the molecular design of efficient enzyme mimetic nitrate reduction reaction catalysts. This kind of catalysts could directly improve the utilization of nitrogen and seed quality in plants.

4 UNIQUE PROPERTIES OF MO-BASED NANOZYMES

Compared to natural enzymes, Mo-based nanozymes with different types are related to their unique physicochemical properties. Generally, to make the nanozymes have higher catalytic activity, three regulation strategies using different thoughts can be employed to promote the binding of nanozymes to substrates by (i) increasing their surface area/volume ratio, (ii) reducing the size of nanozymes, (iii) promoting the preferential exposure of active atoms with catalytic activity, and (iv) increasing the number of suspended bonds.\textsuperscript{67,90} The core goal of these regulation strategies is to improve the exposure degree of the nanozyme active site and its similarity with the structure of active site of natural enzymes. We then describe the tunable enzyme-like activity, stability, and multifunctionality of Mo-based nanozymes based on the physicochemical property (size, morphology, doping, multicomponent synergetic effect, and surface modification)-related structure–function relationship. This physicochemical property-related structure–function relationship is closely relevant to their versatile biomedical applications.
4.1 Tunable enzyme-like activity

4.1.1 Size and morphology

It has been found that the specific enzyme-mimicking catalytic activity of nanozymes can be adjusted by their size, shape, and morphology. First, the catalytic activity of nanozymes can be modulated by tailoring the size. For instance, the electrocatalytic activity of H$_2$O$_2$ by MoS$_2$/GO nanozyme was affected by different thicknesses. The thinner MoS$_2$/GO composites showed higher POD-like catalytic activity than that of thicker one because of

---

**Figure 6** Nitrate reductase (NRase)-like activity of Mo-based nanozymes. (A) An oxo-MoS$_x$ catalyst that serves as an enzyme mimetic nitrate reduction reaction catalyst at neutral pH value. (B) Electrocatalytic activities of oxo-MoS$_x$ and c-MoS$_2$ for NO$_3^-$ reduction at neutral pH. c-MoS$_2$ is a commercially available crystalline MoS$_2$. Reproduced with permission. Copyright 2020, Wiley-VCH
FIGURE 7 Tunable enzyme-like activity based on physicochemical properties including morphology, dopant, integration with other nanomaterials, and surface modifications. (A) TEM images of morphology of MoO$_{3-x}$ NUs and MoO$_{3-x}$ NSs and (B) the UV–Vis absorbance of 1,3-diphenylisobenzofuran (DPBF) reacted with MoO$_{3-x}$ to verify the differences of ROS products. Reproduced with permission. 39 Copyright 2020, American Chemical Society. (C) Enhanced POD-like catalysis activity of N-doped MoS$_2$. Reproduced with permission. 91 Copyright 2020, American Chemical Society. (D) Enhanced POD-like activity of Pt-MoO$_3$ nanocomposite toward colorimetric reaction with TMB. Reproduced with permission. 58 Copyright 2014, The Royal Society of Chemistry. (E) POD-like catalytic activity of the MoS$_2$ NPs toward TMB with different surface modifications. Reproduced with permission. 50 Copyright 2018, The Royal Society of Chemistry.

Faster electron transfer kinetics at thinner MoS$_2$/GO-modified electrode. Second, the shape and morphology of nanozymes play important roles in regulating their catalytic activity. 90 For example, MoO$_{3-x}$ nanourchins (NUs) possessed OXD-like activity to produce $\text{O}_2^{-}$, whereas MoO$_{3-x}$ NSs could not produce measurable levels of ROS (Figures 7A and 7B). 39 In another study, Liu et al. reported that MoO$_3$ nanorods exhibited higher POD-like activity than MoS$_2$ NSs and MoO$_3$ nanowires. 81 The possible reason is that when $\text{H}_2\text{O}_2$ closely contacts with the MoO$_3$ nanorods, the electrons localized at the $p$ orbital of the O atom in $\text{H}_2\text{O}_2$ will be transferred to the $d$ orbital of the
Mo atom, leading to an intense reaction between H$_2$O$_2$ and MoO$_3$ nanorods. Besides, the sufficient gap of the formed rod-like structures was favorable for collision contact between the H$_2$O$_2$ and MoO$_3$ nanorods in the reaction system. These factors may promote the oxidization of H$_2$O$_2$ efficiently. It is worth mentioning that even though the catalytic activity of Mo-based nanozymes can be regulated by their size and morphological changes, the impact of phase structures on their catalytic activity still needs to be deeply investigated.

### 4.1.2 Multicomponent synergistic effect

Hybrid Mo-based nanozymes formed by doping other elements have been developed to maximize the catalytic efficiency. For example, Ce$^{3+}$-doped MoS$_2$ NSs had a strong POD-like activity. The introduction of the Ce$^{3+}$ ions enlarged the interlayer distance of MoS$_2$ NSs, which resulted in a larger number of active sites of MoS$_2$ NSs and accelerated the contact between substrate and catalytic surface, finally improving the kinetics of the catalytic reaction. In addition, the plasma-assisted controllable doping of N into MoS$_2$ NPs (N-doped MoS$_2$ NPs) has been demonstrated to present dramatically enhanced POD-like catalytic activity in contrast to pristine MoS$_2$. The designed N-doped MoS$_2$ NSs could have a lower Fermi level than the pristine MoS$_2$. This is because the N covalently doped into MoS$_2$ could expedite the electron transfer of N-doped MoS$_2$ (Figure 7C). Integrating other nanomaterials such as metals or metal oxides with Mo-based nanozymes also showed improved catalytic activity. For example, because of the synergistic catalytic effects of the three components, the MoS$_2$–polypyrrole (PPy)–Pd nanotubes showed higher POD-like catalytic activity than MoS$_2$, MoS$_2$–PPy, PPy–Pd, and MoS$_2$–Pd nanocomposite. In addition, the Pt–MoO$_3$ hybrid nanomaterial exhibited an enhanced POD-like catalytic activity compared to the MoO$_3$ NSs, Pt NPs, and their physical mixture under the same conditions (Figure 7D). In another study, the MoS$_2$@MgFe$_2$O$_4$ nanocomposite possessed higher POD-like catalytic activity than their two components MgFe$_2$O$_4$ and MoS$_2$. The POD-like activity of MoS$_2$@MgFe$_2$O$_4$ with different component ratios was also investigated. MoS$_2$@MgFe$_2$O$_4$ (42.69 wt% of MoS$_2$) had higher POD-like catalytic activity than MoS$_2$@MgFe$_2$O$_4$ with 23.57 wt% of MoS$_2$ and MoS$_2$@MgFe$_2$O$_4$ with 50.26 wt% of MoS$_2$. As for the kinetic study, the apparent $k_m$ of MoS$_2$@MgFe$_2$O$_4$ with H$_2$O$_2$ as substrate was lower than that of the HRP, NiFe$_2$O$_4$, and MoS$_2$–Pd$_{34}$Ag$_{26}$, implying that MoS$_2$@MgFe$_2$O$_4$ has the highest binding affinity to H$_2$O$_2$. Under optimal conditions, the MoS$_2$@MgFe$_2$O$_4$ can be applied to selectively detect glucose. Other analogous hybrid nanozymes such as AuNPs@MoS$_2$–QDs, Au–Pd/MoS$_2$, MoS$_2$–Pt$_{34}$Au, and TiO$_2$/MoS$_2$ with enhanced POD-like activity have also been developed.

Assembling carbon-based nanomaterials with Mo-based nanozymes to form hybrid nanozymes has also been investigated. As part of much effort, Weng et al. reported that a hybrid of POD-like activity of MoS$_2$ and graphene oxide (MoS$_2$/GO) was used to detect glucose with high sensitivity through the synergistic catalytic effect. The hybrid had the highest catalytic activity when compared with the two components alone and the mixture of two components and HRP. A synergetic POD-like activity was also disclosed for mixed MoS$_2$ QDs and graphene QDs. In short, the above synergistic strategies provide inspiration for improving the catalytic activity of Mo-based nanozymes.

### 4.1.3 Surface modification

Surface modifications also contribute to modulate the catalytic performance of Mo-based nanozymes. Specifically, surface charge and exposure of active sites of nanozymes can affect the catalytic activity, specificity, and stability. At present, Mo-based nanozymes are mostly modified by organic polymers, proteins, and other biopolymers. Our group investigated the POD-like activity of PEGylated MoS$_2$ (PEG-MoS$_2$) NFs. The PEG-MoS$_2$ NSs had improved water dispersibility and stability compared to the undecorated MoS$_2$, which was conducive to the catalysis velocity and affinity for TMB or H$_2$O$_2$, consequently improving the POD-like activity. The PEGylated MoS$_2$ NSs have also been confirmed to possess enhanced POD-like activity. Polyvinylpyrrolidone (PVP) is helpful for the construction of MoS$_2$ nanozyme with high yield, low cost, and good water dispersibility and biocompatibility.

Another typical example for affecting the enzyme-like activity of Mo-based nanozyme is surface charges. In one study, MoS$_2$ (SDS–MoS$_2$) NPs modified with negatively charged sodium dodecyl sulfate (SDS) possessed higher POD-like activity than that of positively charged cetyltrimethylammonium bromide. This is because the negatively charged SDS–MoS$_2$ NPs have strong affinity toward the positively charged TMB substrate. We also compared the POD-like activities of MoS$_2$ NFs modified with positively charged polyethyleneimine (PEI), negatively charged poly(acrylic acid) (PAA), neutrally charged PVP, and positively/negatively charged L-cysteine (Cys) (Figure 7E). The PVP, PAA, and PEI modifications inhibited the catalytic activity of MoS$_2$ NFs, whereas the catalytic activity of the Cys–MoS$_2$ NFs was remarkably promoted toward TMB or ABTS substrate. This could be attributed to the enhanced charge affinity between the Cys–MoS$_2$ NFs.
and positively charged TMB, whereas the Cys on the surface of MoS$_2$ mainly acted as an electron transfer mediator between H$_2$O$_2$ and negatively charged ABTS. Further work also confirmed that the Cys–MoS$_2$ NSs possessed enhanced POD-like activity compared with bulk MoS$_2$.75

Other biomolecules such as oxidized glutathione (GSSG) and hemin have also been used to decorate MoS$_2$ NSs. Both of these compounds can improve the POD-like activity of MoS$_2$ NSs to oxidize TMB substrate.52,57 However, as we mentioned above, the activity of Mo-based nanozymes can sometimes be inhibited by surface modification. That is because the active sites of nanozymes could be shielded by the extra coating or modification and thus their catalytic activity decreases correspondingly.98 Thus, more effort is still needed to develop novel methods to achieve both the colloidal stability in physiological conditions and adequate accessibility to the target substrates especially for biosensing applications.

4.2 Stability

Mo-based nanozymes show improved stability under harsh conditions such as acidic, basic, and high-temperature environments that natural enzymes cannot bear. For instance, the POD-like MoS$_2$ NSs showed a high catalytic activity over a wide pH range (2.0–7.5). The wide pH range could broaden the application of MoS$_2$ NSs in harsh environments.28 In another work, Fe$^{2+}$/MoO$_3$ as a POD-like mimic had favorable thermal stability. When reaction solution was heated to 95°C, the POD-like activity of the nanozyme had almost no change, which can overcome the thermal instability of natural POD. The Fe$^{2+}$/MoO$_3$ had good storage stability in that there was still 85% of POD-like activity when they were stored at 4°C for 20 days.69 In addition, the MoO$_3$ NPs with OXD-like property had superior catalytic performance at pH 2.5 and 70°C.84 More impressively, the hybrid nanozymes MoS$_2$–Pt$_{74}$Ag$_{26}$ had good storage stability in that there was no obvious decrease in catalytic response to H$_2$O$_2$ for 2 months at room temperature.99 The MoS$_2$–Pt$_{74}$Ag$_{26}$ also had good reusability after repeated cycles of H$_2$O$_2$ sensing. Moreover, Yang et al. reported that the MoO$_3$–x nanodots showed higher CAT-like catalytic activity under various conditions such as pH values (3.0–9.0) and temperatures (25–90°C) when compared with CAT.81 Thus, the outstanding stability and catalytic performance of these Mo-based nanozymes enable them beneficial for a broad range of applications even under harsh conditions.

4.3 Multifunctionality

Despite the enzyme-mimicking activity, Mo-based nanomaterials such as MoS$_2$, MoSe$_2$, and MoO$_{3-x}$ also have high photothermal conversion efficiency in the near-infrared (NIR) region because of their specific electronic and optical properties.37,100,101 In recent studies, researchers have found that both PEG-MoS$_2$ NFs and MoS$_2$-hydrogel have good NIR photothermal conversion property and high POD-like activity. The combination of photothermal property and enzyme-like activity makes Mo-based nanomaterials an attractive platform for biomedical applications such as antibacterial and antitumor.

Mo-based nanomaterials can be utilized as a universal carrier for loading other functional molecules or reagents to create biomimetic cascade catalysis system. For example, the POD-like Mo-based nanozyme with immobilized glucose oxidase (GOx) has been constructed for glucose-sensitive colorimetric detection.81 GOx could continuously catalyze the glucose oxidation reaction and produce H$_2$O$_2$ to support the POD-like catalytic activity of nanozyme with high selectivity and acceptable reproducibility. By integrating advantages in the selectivity of natural enzymes with controllable catalytic activity of nanozymes, Mo-based nanozymes can act as vehicles for achieving cascaded reactions. This strategy is also very similar to other biomimetic cascaded nanozymes such as iron-based nanozymes and metal–organic framework nanomaterials.102,103

The hybrid forms of Mo-based nanozymes also endowed them with diverse functionalities. For example, the MoS$_2$/Fe$_3$O$_4$ nanozyme for colorimetric detection of perfluorooctane sulfonate can be recycled by magnetic separation owing to the assembling of Fe$_3$O$_4$ NPs.55 In another work, hybrid Au nanobipyramids with MoS$_2$ (AuNBPs@MoS$_2$) also have the POD-like activity for both anticancer therapy and cellular imaging because of the excellent two-photon luminescence of AuNBPs.43 It deserves to be mentioned that, even though some Mo-based nanomaterials lack obvious enzyme-like activity, they can also be utilized as modulators to disperse and stabilize other artificial nanozymes. For instance, CeO$_2$–PEI-MoS$_2$ NFs have been constructed as nanozymes for cancer photothermal therapy. The CeO$_2$ NPs mimicked multienzyme such as SOD, CAT, and Fenton-like catalyst properties, whereas MoS$_2$ NFs acted as supports of CeO$_2$ NPs and photothermal agents.36 All these features indicate that Mo-based nanomaterials pave a way for the fabrication of multifunctional nanozymes for broad applications, especially in the field of biomedicine.
Mo-based nanozymes hold great promise for biosensing and biodetection, cancer therapy, and combating bacteria (Table 2). In the following section, we discuss the representative applications of Mo-based nanozymes.

## 5.1 Biosensing and biodetection

### 5.1.1 In vitro sensing and biodetection

Most Mo-based nanozymes biosensors are focused on detecting bioactive molecules such as small biomolecules (e.g., H₂O₂, glucose, cholesterol, and glutathione [GSH]), disease biomarkers, and biological toxic substances. First of all, many studies have demonstrated that Mo-based nanozymes can be utilized as H₂O₂ and glucose biosensors via the colorimetric assay. The usual approach is monitoring the colorimetric reactions of some substrate (e.g., TMB and ABTS) that is primarily oxidized by *OH generated in the nanozyme catalytic reaction. For instance, our group constructed a biosensor based on the POD-like activity of Cys–MoS₂ NFs (Figures 8A and 8B). The Cys–MoS₂ NFs presented high catalytic activity against H₂O₂ in the presence of TMB or ABTS. The concentration of H₂O₂ can be determined by measuring the absorbance change of oxTMB induced by the catalytic reaction of Cys–MoS₂ NFs. Because H₂O₂ is produced when GOx efficiently catalyzes the oxidation of glucose, a glucose detection system was established by the Cys–MoS₂ NFs to replace natural POD. The limit of detection (LOD) for H₂O₂ and glucose was 4.103 and 33.51 μM, respectively, which is suitable for biomedical diagnosis. Similarly, Weng et al. developed an efficient colorimetric assay based on POD-like MoS₂/GO hybrid to detect H₂O₂ and glucose in serum samples with or without visible light. They demonstrated that the LOD for H₂O₂ and glucose can be reduced to 2.5 and 65 nM, respectively, with visible light. More interestingly, the MoO₃/C nanorods with POD-like catalytic activity have been used to detect H₂O₂. The LOD was calculated to be 0.181 μM, which is lower than those for magnetic Fe₃O₄ NPs (3.0 μM), α-AgVO₃ microrods (2.0 μM), and V₂O₃-OMC (1.7 μM).

Electrochemical methods are also considered as promising strategies for highly selective, sensitive detection of H₂O₂. An enzyme-free electrochemical sensor was fabricated by electrochemical deposition of Au–Pt bimetallic NPs on the MoS₂ NFs surface. The MoS₂–Au/Pt nanocomposites exhibited promising catalytic activity for specific detection of H₂O₂. The enzyme-free electrochemical sensor had wide linear range and high sensitivity.

The MoS₂–Au/Pt electrochemical sensor was further successfully used to detect H₂O₂ in real serum samples. Very recently, another enzyme-free electrochemical sensor based on a porous Mo₂C impregnated in N-doped carbon (p-Mo₂C/NC) has been designed toward H₂O₂ detection. The excellent biomimetic performance can be attributed to the porous Mo₂C catalyst rather than conventionally relying on only catalyst dispersed in a porous substrate with a large reaction surface area.

Despite H₂O₂ and glucose, another biomolecule cholesterol has also been sensed by Mo-based nanozymes using the colorimetric method. For instance, our group fabricated GSSG-modified MoS₂ NSs (MoS₂-GSSG NSs) with high POD-like catalytic activity, which could serve as colorimetric sensor for detection of H₂O₂ and cholesterol. The cholesterol was catalyzed by cholesterol oxidase (ChOx) in the presence of O₂ to generate H₂O₂, which supports the catalysis of MoS₂-GSSG NSs to accelerate the oxidation of TMB. In addition, the Mo-based nanozymes can be used to detect reductive small biomolecules such as GSH, Cys, vitamin B₁, and lipase, which can inhibit the enzyme-like activity of nanozymes in the presence of dual substrates such as TMB and H₂O₂ (Figure 8C).

By monitoring the degree of color fading of organic substrates, these reductive small biomolecules can be quantitatively detected.

Mo-based nanozymes have also been used to detect disease biomarkers. In particular, development of effective methods for rapid and accurate detection of cancer-related antigens is significant for cancer diagnosis. For example, a MoS₂@Cu₂O–Pt nanohybrid as an enzyme-mimetic label was used to construct an ultrasensitive sandwich-type electrochemical immunosensor to detect hepatitis B surface antigen. A novel MoS₂/PtCu nanocomposite with excellent OXD-like activity has been constructed for detection of cancer cells. The nanocomposites quickly catalyzed the oxidation of three common chromogenic substrates such as TMB, ABTS, and OPD in the presence of dissolved oxygen in solution, producing typical colors. On the basis of OXD-like activity of MoS₂/PtCu and mucin 1 (MUC1) aptamer, selective binding of aptamer-conjugated MoS₂/PtCu aptasensor (apt-MoS₂/PtCu) on the MUC1-overexpressed cells converted the recognition process into a quantitative colorimetric signal. The apt-MoS₂/PtCu showed good sensitivity and selectivity to targeting can...
| Nanozyme                        | Activity/Mechanism | Biomedical applications                                                                 | Reference |
|--------------------------------|--------------------|----------------------------------------------------------------------------------------|-----------|
| MoS$_2$ NSs                    | POD                | Detection of H$_2$O$_2$, glucose, copper ions, iron(II) ions, Cr(VI) ions, mercury(II) ions, and label-free lipase | 40,50,68,109,117,152 |
| MoS$_2$/GO hybrid              | POD                | H$_2$O$_2$ and glucose                                                                  | 35        |
| Single-atom Co-MoS$_2$         | POD                | Detection of H$_2$O$_2$                                                                  | 82        |
| MoS$_2$–Au/Pt hybrid           | POD                | Detection of H$_2$O$_2$                                                                  | 54        |
| Aptamer-MoS$_2$/PtCu hybrid    | OXD/POD            | Detection of cancer cells                                                                | 74        |
| Mo$_2$O$_3$–based hybrid       | POD                | Detection of ovarian cancer biomarker                                                    | 153       |
| PEG-MoO$_3$–NSs                | OXD                | Detection of vitamin B1                                                                  | 79        |
| TiO$_2$/MoS$_2$ hybrid         | POD                | Detection of glutathione                                                                 | 94        |
| Mo$_2$O$_3$ NPs                | POD                | Detection of acetylcholinesterase inhibitor tacrine                                     | 31        |
| MnO$_2$ NS-assisted MoS$_2$ QDs/OPD | POD    | Fluorometric detection and cellular imaging of glutathione                               | 150       |
| Mo$_2$S$_2$@Cu$_2$O–Pt hybrid  | POD                | Detection of the Hepatitis B surface antigen                                             | 104       |
| Mo$_2$S$_2$ GSSG NSs           | POD                | Detection of H$_2$O$_2$ and Cholesterol                                                  | 52        |
| Mo$_2$S$_2$–PPy–Pd hybrid      | POD                | Detection of cysteine                                                                   | 92        |
| Mo$_2$S$_2$–Au@Pt hybrid       | POD                | Detection of cysteine                                                                   | 154       |
| MoSe$_2$ NSs                   | POD                | Detection of H$_2$O$_2$ and xanthine                                                    | 50        |
| OPD-MoS$_2$ NSs                | POD                | Detection and imaging of intracellular H$_2$O$_2$                                       | 148       |
| Mo$_2$S$_2$–Pt$_3$Au$_1$ hybrid | POD                | Detection of phenol                                                                     | 53        |
| Cys–Mo$_2$ NSs                 | POD                | Detection of trinitrotoluene                                                            | 75        |
| CS-MoSe$_2$ NSs                | CAT                | Detection of Mercury(II)                                                              | 116       |
| Fe$^{2+}$/MoO$_3$ NSs           | POD                | Detection of H$_2$O$_2$ and triacetone triperoxide (TATP) explosives                   | 69        |
| Three-dimensional MoS$_2$/Fe$_3$O$_4$ hybrid | POD    | Detection of perfluorooctane sulfonate                                                   | 55        |
| Mo$_2$S$_2$–COOH-MWCNT nanohybrid | OXD              | Detection of 5-nitroguaiacol sodium                                                    | 155       |
| MoO$_3$–x NUs                  | CAT/OXD            | Tumor-specific cascade catalytic therapy                                                | 39        |
| AuNBPs@MoS$_2$ NSs             | POD                | Anticancer therapy                                                                      | 151       |
| Fe$_3$O$_4$@MoS$_2$–Ag hybrid  | POD                | Antibacterial                                                                           | 156       |
| Mo$_2$S$_2$–hydrogel           | POD                | Antibacterial and promoting wound healing                                               | 135       |
| PEG–Mo$_2$ NPs                 | POD                | Antibacterial and promoting wound healing                                               | 27        |
| N-doped Mo$_2$ NSs             | POD                | Antibacterial and promoting wound healing                                               | 61        |
| MoO$_3$–x nanodots             | POD                | Antibacterial and promoting wound healing                                               | 157       |
| Mo$_2$S/rGO vertical heterostructure | OXD/POD/CAT  | Antibacterial and promoting wound healing                                               | 64        |
| Cu$_2$Mo$_2$ nanoplates         | OXD/POD            | Eradication of multidrug-resistant bacteria                                               | 138       |
| Mo$_2$O$_3$ NPs                | OXD                | Therapeutic for sulfite oxidase deficiency                                                | 42        |
| Mo$_2$S NSs                    | SOD/CAT/POD        | Protect cells against oxidative injury caused by H$_2$O$_2$                             | 43        |
| Fullerene-like MoS$_2$ NPs     | SOD/CAT            | Antioxidant abilities of artificial synovial fluid                                       | 86        |
| TPP-MoS$_2$ QDs                | SOD/CAT            | Alzheimer’s disease                                                                     | 139       |
| MoO$_3$–x nanodots             | CAT/SOD            | Modulators for amyloid assembly and neurotoxicity                                         | 41        |
**FIGURE 8** Mo-based nanozymes for biosensing. (A) Photos of chromogenic solutions for different concentrations of glucose using Cys–MoS$_2$ NFs and ABTS as a chromogenic substrate. (B) The corresponding calibration curves by monitoring the absorbance at 414 nm. Reproduced with permission.\(^{50}\) Copyright 2018, The Royal Society of Chemistry. (C) Oxygen vacancy-engineered PEGylated MoO$_3$–x NPs with sulfite oxidase mimetic activity for vitamin B1 detection. Reproduced with permission.\(^{79}\) Copyright 2019, WILEY-VCH. (D) A field-portable and colorimetric CS-MoS$_2$ NSs sensor for the visual detection of Hg$^{2+}$. Reproduced with permission.\(^{116}\) Copyright 2019, American Chemical Society. (E) Molybdenum-polysulfide (MoSx)-deposited nickel–iron bimetal Prussian-blue-analog-based hollow nanocages for an online sensing platform to optically detect hydrogen sulfide (H$_2$S) in the brains of living rats. Reproduced with permission.\(^{120}\) Copyright 2020, American Chemical Society.
cer cells. In another study, an ultrasensitive electrochemical circulating tumor cells (CTCs) detection strategy was developed based on reduced graphene oxide/molybdenum disulfide (rGO/MoS2) NSs and immunomagnetic beads Fe3O4 NPs dual enzyme mimics synergistic catalysis for signal amplification. The Fe3O4 NPs acted as separation and enrichment CTCs as well as enzyme mimics with rGO/MoS2 synergistic catalysis for signal amplification in cytosensors. The rGO/MoS2 synergistic catalysis with Fe3O4 NPs showed good electrocatalytic activity toward H2O2. The proposed electrochemical biosensor could detect human breast carcinoma cells (MCF-7) down to 6 cells mL−1 with a linear range from 15 to 45 cells mL−1 at the acceptable stability condition and reproducibility.

The exposure of biological toxic substances in the environment will directly or indirectly affect human health. Therefore, detections of the toxic substances are major and long-standing problems. Some metal ions (e.g., Hg2+, Cu2+, Cr6+, and Fe2+)40,68,116,117 and organic compounds (e.g., phenol, perfluorooctane sulfonate, trinitrotoluene, triacetone triperoxide [TATP] explosives, and carbendazim [CBZ]) in wastes and foods have been detected by Mo-based nanozymes. For example, a field-portable and colorimetric sensor for the visual detection of Hg2+ has been constructed using safe chitosan-modified MoSe2 NSs (CS-MoSe2 NSs) nanozyme (Figure 8D).116 The POD- and OXD-like activities of CS-MoSe2 NSs were significantly promoted after the addition of Hg2+. That is because that the Hg2+ can be captured by chitosan molecules and partially reduced to be Hg0 on the surface of CS-MoSe2 NSs. Then, in situ formed Hg0 altered the surface properties and enhanced the binding affinity of CS-MoSe2 NSs for TMB substrate to produce higher catalytic activities. This CS-MoSe2 NSs-based system could be utilized to determine the Hg2+ concentration by monitoring Hg2+-induced changes of the UV–Vis absorbance peaks of the blue oxTMB. More meaningfully, the Hg2+ in real water and serum samples can be determined by integrating the CS-MoSe2 NSs and smartphone. Moreover, MoSe2 NSs with POD-like activity were developed to detect Cu2+ ions in drinking water because the Cu2+ can inhibit the catalytic activity of MoSe2 NSs. The LOD value was 92 nM, which is much lower than that of Cu2+ in drinking water.117 Ni et al. have reported a selective fluorescent catalytic biosensor based on layered POD-like MoSe2 NSs for the detection of Fe2+. The Fe2+ could significantly activate MoSe2 NSs to catalyze the oxidation of OPD to generate a fluorescent product 2,3-diaminophenazone. The MoSe2/OPD/H2O2 biosensor showed a significantly enhanced fluorescence signal in the presence of Fe2+ in real water samples.

Aside from the potentially harmful metal ions mentioned above, certain organic compounds in wastes have been detected by Mo-based nanozymes. Recently, uniform Pt3Au1 NPs-decorated few-layer MoS2 NSs were fabricated as nanozymes to detect phenol, which is a common environmental pollutant in waste water.53 The MoS2–Pt3Au1 nanocomposite displayed enhanced POD-like activity compared to pure MoS2 NSs. The fast and selective colorimetric detection of phenol was based on oxidative coupling reaction of phenol and 4-aminoantipyrine in the presence of H2O2 as an oxidant to form pink color product. In addition, the POD-like Fe2+/MoO3 NSs were constructed to visually colorimetric detect TATP explosives.69 Because H2O2 is the main product of the acidic hydrolysis of TATP explosive, Fe2+/MoO3 NSs with good selectivity for H2O2 can visually detect as low as 60 μM of TATP.

Mo-based nanozymes also play an important role in food safety sensors. In a very recent study, CBZ residues in tea and rice samples have been determined by an electrochemical nanozyme sensor that was coupled with machine learning for intelligent analysis. This nanozyme sensor was composed of carboxymethyl cellulose (CMC)-modified graphene-like MoS2/multiwalled carbon nanotubes (MWCNTs) porous nanohybrid network (CMC-MWCNTs/MoS2) with OXD-like activity.118 The reciprocal of the CBZ concentration was positively correlated with the peak current, which is a typical kinetic characteristic of the biological enzyme. This electrochemical nanozyme sensor can sensitively determine CBZ with a wide linear range of 0.04–100 μM and low LOD of 7.4 nM. Thus, the proposed sensor system may play a significant role in the development of intelligently analyzing CBZ residues in agricultural products.

### 5.1.2 In vivo sensing and detection

A number of Mo-based nanozymes for in vivo sensing have also been developed. Very recently, molybdenum-polysulfide (MoSx)-deposited nickel–iron bimetal Prussian-blue-analog-based hollow nanocages (Nanocages) with POD-, CAT-, and laccase-like activities were fabricated.120 The POD- and CAT-like activities could scavenge ROS in cells (scavenging excess H2O2 and regulate H2O2 signals during oxidative stress). On the other side, the nanocages with laccase-mimicking activity have been integrated with an online sensing platform to optically detect hydrogen sulfide (H2S) in the brains of living rats (Figure 8E). It was suggested that the primary mechanism of detection was H2S etching the reduced laccase-like activity of the nanocages, whereas the oxidation product offered the read-out signals. This finding may provide an opportunity for upgrading the design strategy of nanozyme-based in vivo detection methods. In another study, Lin et al. constructed CoMo hybrids with OXD-, POD-, and CAT-like activities by epitaxial growth
of the MoS\textsubscript{2} nanosponge on Co(OH)\textsubscript{2} NFs surface.\textsuperscript{121} The OXD-mimicking activity of the CoMo hybrids can catalyze the oxidation of TMB and then the produced oTMB induced by the OXD-like catalytic reaction can selectively oxidized ascorbic acid. The proposed colorimetric strategy has been successfully utilized to measure ascorbic acid in rat brains during the cerebral calm/ischemia process.

### 5.2 Cancer therapy

Mo-based nanomaterials are desirable candidates for effective cancer therapy such as photodynamic therapy, photothermal therapy, chemotherapy, radiotherapy (RT), and immunotherapy.\textsuperscript{4,122,123} Based on the catalytic properties of Mo-based nanozymes, some promising strategies have been developed for cancer therapy by modulating ROS production. In a very recent study, Ling et al. designed biodegradation-mediated MoO\textsubscript{3−x} NUs with tunable enzyme-mimicking activity, which could selectively exert therapeutic effect via cascaded catalytic reactions in the tumor microenvironment (TME).\textsuperscript{39} Meanwhile, normal tissues were not harmed due to the responsive biodegradation of MoO\textsubscript{3−x} NUs in the physiological environment (pH ∼ 7.4) (Figure 9A). In particular, the MoO\textsubscript{3−x} NUs first exhibited CAT-like activity to catalyze the decomposition of H\textsubscript{2}O\textsubscript{2} in TME, generating abundant O\textsubscript{2} for triggering subsequent OXD-like activity. Then, plenty of cytotoxic O\textsubscript{2}•− was produced for tumor cell death. This study demonstrated a biodegradation-mediated in vivo catalytic activity-regulated nanozyme for cascaded catalytic therapy of tumor.

TME-mediated nanocatalytic strategy of Mo-based nanozyme is promising for improving antitumor effect. Very recently, our group designed a cascaded nanocatalytic reactor (MoS\textsubscript{2}@CGTC NCR) with response to glucose. The NCR loaded GOx and chemotherapeutic drug tirapazamine (TPZ) together on the surface of MoS\textsubscript{2} nanzyme carrier for regulating TME to realize self-enhanced chemocatalytic therapy (Figure 9B).\textsuperscript{124} Based on the ultrahigh intratumoral glucose concentration, the MoS\textsubscript{2}@CGTC NCR could persistently regulate TME through oxidizing glucose to produce gluconic acid and H\textsubscript{2}O\textsubscript{2}, while quickly consuming O\textsubscript{2} to activate chemotherapeutic TPZ. Then, the subordinate POD-like catalytic efficacy of MoS\textsubscript{2} could be remarkably boosted by the self-supplied H\textsuperscript{+} and H\textsubscript{2}O\textsubscript{2} markedly boosted, producing plenty of •OH for nanocatalytic therapy. In the meantime, the MoS\textsubscript{2} nanzyme also depleted GSH to decrease •OH consumption. Hence, this study provides highly promising protocols for combined chemotherapy with cascaded nanocatalytic therapy.

Moreover, RT is still one of the widely used first-line treatment for cancers in clinic. Currently, it is highly desirable to develop efficient nanoradiosensitization system that enhances radiation doses in cancer cells to sensitize RT while sparing normal tissues. Very recently, our group designed a TME-responsive disassembled small-on-large molybdenum disulfide/hafnium dioxide (MoS\textsubscript{2}/HfO\textsubscript{2}) dextran (M/H-D) nanoradiosensitizer (Figure 9C).\textsuperscript{125} The M/H-D can release the HfO\textsubscript{2} NPs in TME to enhance tumor penetration of the HfO\textsubscript{2} NPs upon NIR exposure, which can solve the bottleneck of insufficient internalization of the HfO\textsubscript{2} NPs. The POD-like catalytic efficiency of M/H-D nanoradiosensitizer could also be increased upon the NIR photothermal exposure, which selectively catalyzed intratumorally overexpressed H\textsubscript{2}O\textsubscript{2} into highly toxic •OH. This TME-responsive precise nanoradiosensitization has achieved improved irradiation effectiveness, potent oxygenation in tumor, and efficient suppression to tumor, which can also be guided by computed tomography and photoacoustic imaging in real time.

### 5.3 Combating bacteria

Bacterial infections are an ever-growing global crisis with devastating consequences to public health care. Besides the most widely accepted treatment paradigm using antibiotics, nanozymes have been used as powerful antibacterial agents. Recently, 2D materials such as graphene,\textsuperscript{126,127} TMDCs,\textsuperscript{128} black phosphorus,\textsuperscript{129} layered double hydroxides,\textsuperscript{130} and transition metal carbides and nitrides (MXenes)\textsuperscript{131} have been intensively explored for antimicrobial applications on account of their superior physicochemical properties.\textsuperscript{132} For example, the reduction of layers of 2D nanomaterials can enhance their antimicrobial activity.\textsuperscript{133} Among these 2D nanomaterials, Mo-based TMDCs such as MoS\textsubscript{2} and MoSe\textsubscript{2} can also act as nanozymes to eliminate bacteria.\textsuperscript{134–136} The underlying antibacterial mechanism of Mo-based nanozymes is to produce ROS to damage bacteria during the mimic enzyme catalytic reaction. Additionally, the few-layered MoS\textsubscript{2} or MoSe\textsubscript{2} can generate a large number of atomically sharp edges, more active sites, larger surface to volume ratio, and higher photothermal therapy efficacy, all of which contribute to oxidative stress and membrane damage to bacteria. Recently, our groups fabricated a biocompatible PEG-MoS\textsubscript{2} NFs with a rough surface as synergistic antibacterial system, which possessed good bacterial trapping capacity, high POD-like catalytic activity, and NIR photothermal conversion efficacy (Figures 10A and 10B).\textsuperscript{27} This POD-like catalyst decomposed low concentration of H\textsubscript{2}O\textsubscript{2} to produce highly toxic •OH, which can destroy the integrity of bacterial cell walls. Taking advantage of the PEG-MoS\textsubscript{2}}
FIGURE 9  Mo-based nanozymes for cancer therapy. (A) Schematic illustration of biodegradation-mediated enzymatic activity-tunable molybdenum oxide nanourchins (MoO$_{3-x}$ NUs) with the highly specific toxicity to tumor tissues via a multienzyme stepwise cascade catalysis in acidic tumor microenvironment. Reproduced with permission.$^{39}$ Copyright 2020, American Chemical Society. (B) Glucose-responsive cascaded nanocatalytic reactor (MoS$_2$@CGTC NCR) with self-modulated tumor microenvironment for enhanced chemocatalytic therapy. Reproduced with permission.$^{124}$ Copyright 2020, The Royal Society of Chemistry. (C) Stimuli-responsive small-on-large nanoradiosensitizer (MoS$_2$/HfO$_2$-dextran) for enhanced tumor penetration and radiotherapy sensitization. Reproduced with permission.$^{125}$ Copyright 2020, American Chemical Society.

NFs-mediated generation of •OH and hyperthermia, this strategy eliminated both Gram-negative ampicillin resistant Escherichia coli (Amp$^+$ E. coli) and Gram-positive endospore-forming Bacillus subtilis rapidly and effectively. This versatile synergetic antibacterial strategy can efficiently promote the dermal disinfection and wound healing in vivo. In our subsequent study, N-doped defect-rich MoS$_2$ NSs (N-MoS$_2$) with enhanced POD-like catalytic activity have also been fabricated for antibacterial applications.$^{61}$ The N-MoS$_2$ NSs could catalyze H$_2$O$_2$ of impaired bacteria induced by sharp edges of NSs to produce more •OH. Consequently, they can effectively kill
E. coli and B. subtilis as well as promote bacteria-infected wound healing in vivo.

To increase biocompatibility of MoS2 nanozymes, a positively charged and multiporous MoS2-hydrogel for effective antibacterial activity was further proposed by Qu et al.135 The MoS2-hydrogel exhibited POD-like catalytic ability and NIR photothermal property. The POD-like MoS2 NFs assembled on the hydrogel could produce \( \cdot \)OH from the catalytic decomposition of H\(_2\)O\(_2\) to partially kill bacteria, whereas the MoS2-hydrogel could capture and confine the bacteria in the region of ROS destruction to strengthen the antimicrobial efficiency (Figure 10C–E). More importantly, by combining the NIR photothermal property and catalytic ability of nanozymes, the nanozyme-hydrogel can achieve a synergistic bactericidal effect. The dermal wound healing rate was accelerated...
by this strategy. In a further study, Qu et al. also found that MoS\textsubscript{2} NSs can vertically align on copper substrate, simultaneously resulting in a rough surface to capture bacteria and more active defect-rich edge sites to improve POD-like activity.\textsuperscript{137} This nanozyme possessed increased antibacterial activity against both \textit{E. coli} and \textit{S. aureus}. Very recently, Wang et al. reported a new near-infrared II light-responsive \textsubscript{Cu},MoS\textsubscript{2} nanozyme with enhanced OXD- and POD-like catalytic activities to improve ROS generation for highly efficient killing of bacteria.\textsuperscript{138} Although the abovementioned Mo-based nanozymes have been successfully employed to combating bacteria, more effort is required to focus on designing novel Mo-based nanozymes for combating more types of drug-resistance bacteria, promoting long-term wound healing, antibiofilm, and antibiofouling.

5.4 | Others applications

Despite the abovementioned applications, several studies have also demonstrated Mo-based nanozymes for treatment of Alzheimer's disease (AD). AD is a progressive disorder that causes brain cells to degenerate and die, which is triggered by the accumulation of amyloid beta (A\textsubscript{β}) and oxidative stress. AD therapy can be successfully performed by regulating the catalytic activity of Mo-based nanozymes with antioxidant properties. Recently, Hu’s group designed a novel TPP-conjugated 1,2-distearoyl-sn-glycero-3-phosphethanolamine-N-[amino(polyethyleneglycol)-2000]-functionalized MoS\textsubscript{2} (TPP-MoS\textsubscript{2}) QDs to target the mitochondria in microglia.\textsuperscript{139} TPP-MoS\textsubscript{2} QDs with CAT- and SOD-like activities can cross the blood–brain barrier (BBB), then escape from lysosomes, and target mitochondria of the microglia. It has been demonstrated that the TPP-MoS\textsubscript{2} QDs with dual enzyme activity possess the ability to eliminate ROS mainly produced in mitochondria. The neuron protection was accomplished by the synergistic effects of scavenging ROS, downregulating the proinflammatory cytokines IL-1\textbeta, IL-6, and TNF-\textalpha and upregulating TGF-\beta. Moreover, the TPP-MoS\textsubscript{2} QDs facilitated microglial polarization from the inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, which was conductive to the protection of neurons. It has been well recognized that proteolysis of A\textsubscript{β} peptides is a promising approach against AD. Accordingly, Qu’s group constructed a high-efficiency A\textsubscript{β}-degrading artificial metalloprotease (MoS\textsubscript{2}-Co) using a MoS\textsubscript{2} NSs and a cobalt complex of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Codota).\textsuperscript{140} By binding to the A\textsubscript{β} peptide, MoS\textsubscript{2}-Co can inhibit the formation of \beta-sheet structures and shorten the distance between cobalt complex and A\textsubscript{β} peptides. Moreover, MoS\textsubscript{2}-Co can generate local heat upon NIR irradiation to destabilize the \beta-sheet structures of A\textsubscript{β} aggregates. Furthermore, the designed MoS\textsubscript{2}-Co can significantly reduce A\textsubscript{β}-mediated cytotoxicity and cross the BBB. This method may inspire the design of artificial nanozymes for degrading amyloids.

6 | CONCLUSIONS, CHALLENGES, AND FUTURE PERSPECTIVES

Construction of Mo-based nanozymes mimicking the catalytic function of natural enzymes is a challenging task. Elucidation of the relationship between the physicochemical properties and their enzyme-like activities is of great importance in the development and design of Mo-based nanozymes. We have summarized the progress in the development of bioinspired Mo-based nanozymes mainly including POD, OXD, CAT, SOD, and so on. These kinds of Mo-based nanozymes were constructed via various synthesis strategies with physicochemical properties (size, surface modification, morphology, and so on)-related enzyme-like activities and catalytic mechanisms. Especially, the fundamental of its different biomedical applications for biosensing and biodetection, cancer therapy, and combating bacteria is based on the reversible conversion between valence states of Mo(IV)/Mo(V)/Mo(VI), which endows Mo-based nanozymes with both anti- and pro-oxidative properties. However, a number of critical issues still need to be addressed for further development of Mo-based nanozymes.

6.1 | Challenges in developing new types of Mo-based nanozymes

Further ground-breaking research is required, including improvement in the synthetic techniques to enable high-throughput and affordable synthesis of nanozymes with controlled structures and properties. Moreover, although Mo-based nanozymes have been reported to mimic several enzymes, the research on Mo-based nanozymes mainly focuses on POD-like catalytic activity. Future effort needs to be devoted to exploring new Mo-based nanozymes to mimic other natural enzymes. Thus, the optimal design, controllable preparation, and standardization of Mo-based nanozymes are very important, consequently reducing the learning cycle in nanzyme research and saving development costs. In addition, single-atom nanzymes catalysts can be considered as the limit in the precise design of nanomaterials at the atomic level. Their structural simplicity and homogeneity can facilitate precise identification and characterization of active sites. Thus, design of Mo-based nanozymes with high activity and selectivity by
single-atom strategy also represents a novel and promising avenue.141

6.2 Challenges in catalytic activity, mechanisms, and biological effect studies

Mo-based nanozymes can serve as either oxidants or antioxidants in various applications. Generally, some Mo-based nanozymes with POD- and OXD-like activities that can produce ROS have been studied as oxidants, whereas others with CAT- and SOD-like activities that can scavenge ROS have been investigated as antioxidants. The impacting factors of the various catalytic activities including external or internal physicochemical properties of Mo-based nanozymes are still required to be further clarified. Moreover, the catalytic specificity and substrate selectivity of Mo-based nanozymes should be considered. Besides adjusting the type of surface modification and the local density of ligands to improve the exposure degree of the active enzyme site, an alternative approach related to the improvement the catalytic activities the introduction of molecular structure of the active site into natural enzymes to nanozymes. In the future, the two most possible forward-looking ideas for design of Mo-based nanozymes are as follow. (i) The introduction of stimulus-responsive components could provide possibilities for further improving the enzyme-like activity of Mo-based nanozymes. (ii) The synergistic effect of multicomponent such as single atom, dopants, oxides, metals, carbon, polymer, and so on can be used to form Mo-based hybrids to maximize the catalytic efficiency. In addition, collaborative effort from various disciplines, such as computational studies, machine learning, and artificial intelligent techniques, may help to address the deep mechanism study challenge. Furthermore, the molecular imprinting technology may be used to enhance the selectivity of Mo-based nanozymes.142 More importantly, when administrated into living organisms, the biological fate such as final biodegradation products, pharmacokinetics, and immunogenicity of Mo-based nanozyme systems has not been systematically investigated. Further studies about assessments of cellular role of nanozymes at a relevant dosage, preclinical toxicity under typical conditions, as well as worst case scenarios, with and without appropriate safeguards, are still needed. Especially, understanding the specificity of nano–bio interactions and the corresponding biological responses is of great importance from the perspective of corona and redox reactions in view of the variable oxidation states of the biospired Mo-involved nanozymes. In conclusion, we believe that systemically administered Mo-based nanozymes still need optimization to be fully accepted in the clinic for disease therapy; however, Mo-based nanozymes that are locally administered as antibacterial will soon find their way to the market.

6.3 Challenges in broad catalytic applications

Currently, Mo-based nanozymes have been used for biosensing, cancer therapy, combating bacteria, detection of environmental pollutants, and other antioxidant applications. Coupling the characteristics of the tumor microenvironment (such as acidic pH, hypoxia, and tumor stem cells) with the unique properties of Mo-based nanozymes may inspire us to create novel nanozymes for more effective cancer treatment. Taking advantage of their abilities to traverse the BBB and scavenge ROS, Mo-based nanozymes have the potential to be utilized for therapy of brain diseases (stroke and Parkinson’s disease). They are also expected to have more other biomedical applications in preclinical and clinical phases such as more effective elimination of biofilms, gene editing, and nanorobots in future.143,144

We hope that this review will play some imperative role in assisting future developments in biocatalytic field. We and other researchers will continue to explore this promising nanozyme. The unique properties of Mo-based nanozymes and numerous ways in which the properties can be tuned by their variable oxidation states will likely lead to the development of more exciting stand-alone techniques and effective combinations of existing ones.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by the National Basic Research Programs of China (2016YFA0201600), National Natural Science Foundation of China (51772293, U1932112), Beijing Natural Science Foundation (2202064), CAS Key Laboratory of Nano-BioInterface (20NBI01), Natural Science Foundation of Ningxia (2020AAC03115), and Scientific Research Project of the Ningxia Higher Education Institutions of China (NGY2020034).

ORCID

Wenyan Yin https://orcid.org/0000-0001-6726-3938

REFERENCES

1. Y. Chen, G. Zhang, Q. Ji, H. Liu, J. Qu, ACS Appl. Mater. Inter. 2019, II, 26781.
2. X. Hu, W. Zhang, X. Liu, Y. Mei, Y. Huang, Chem. Soc. Rev. 2015, 44, 2376.
130. K. Ma, Y. Li, Z. Wang, Y. Chen, X. Zhang, C. Chen, H. Yu, J. Huang, Z. Yang, X. Wang, ACS Appl. Mater. Inter. 2019, 11, 29630.
131. Arabi Shamsabadi, M. Sharifian Gh, B. Anasori, M. Soroush, ACS Sustain. Chem. Eng. 2018, 6, 16586.
132. L. Mei, S. Zhu, W. Yin, C. Chen, G. Nie, Z. Gu, Y. Zhao, Theranostics 2020, 10, 757.
133. J. Zheng, J. Li, L. Zhang, X. Chen, Y. Yu, H. Huang, J. Mater. Sci. 2020, 55, 7226.
134. X. W. Huang, J. J. Wei, T. Liu, X. L. Zhang, S. M. Bai, H. H. Yang, Nanoscale 2017, 9, 17193.
135. Y. Sang, W. Li, H. Liu, L. Zhang, H. Wang, Z. Liu, J. Ren, X. Qu, Adv. Funct. Mater. 2019, 29, 1900518.
136. D. Ma, C. Xie, T. Wang, L. Mei, X. Zhang, Z. Guo, W. Yin, Chem-BioChem 2020, 21, 2373.
137. F. Cao, L. Zhang, H. Wang, Y. You, Y. Wang, N. Gao, J. Ren, X. Qu, Angew. Chem. Int. Edit. 2019, 58, 16236.
138. J. Shan, K. Yang, W. Xiu, Q. Qiu, S. Dai, L. Yuwen, L. Weng, Z. Teng, L. Wang, Small 2020, 16, 2001099.
139. C. Ren, D. Li, Q. Zhou, X. Hu, Biomaterials 2019, 232, 119752.
140. M. Ma, Y. Wang, N. Gao, X. Liu, Y. Sun, J. Ren, X. Qu, Chem. Eur. J. 2019, 25, 11852.
141. S. Lin, H. Wei, Sci. China Life Sci. 2019, 62, 710.
142. Z. Zhang, X. Zhang, B. Liu, J. Liu, J. Am. Chem. Soc. 2017, 139, 5412.
143. M. Hu, X. Ge, X. Chen, W. Mao, X. Qian, W. E. Yuan, Pharmaceutics 2020, 12, 665.
144. J. R. Pettree, K. Yehl, K. Galior, R. Glazier, B. Deal, K. Salaita, ACS Chem. Biol. 2018, 13, 215.
145. K. Inzani, M. Nemattollahi, F. Vullum-Bruer, T. Grande, T. W. Reenaas, S. M. Selbach, Phys. Chem. Chem. Phys. 2017, 19, 9232.
146. M. M. Liu, S. H. Li, D. D. Huang, Z. W. Xu, Y. W. Wu, Y. Lei, A. L. Liu, Sensor. Actuat. B-Chem. 2020, 305, 127512.
147. Y. Zhao, Y. Huang, J. Wu, X. Zhan, Y. Xie, D. Tang, H. Cao, W. Yun, RSC Adv. 2018, 8, 7252.
148. H. Liu, B. Wang, D. Li, X. Zeng, X. Tang, Q. Gao, J. Cai, H. H. Cai, Microchim. Acta 2018, 185, 287.
149. W. Dong, G. Chen, X. Hu, X. Zhang, W. Shi, Z. Fu, Sensor. Actuat. B-Chem. 2020, 305, 127530.
150. X. Tang, X. Zeng, H. Liu, Y. Yang, H. Zhou, H. Cai, Microchim. Acta 2019, 186, 572.
151. S. K. Maji, S. Yu, K. Chung, M. Sekkarapattai Ramasamy, J. W. Lim, J. Wang, H. Lee, D. H. Kim, ACS Appl. Mater. Inter. 2018, 10, 42068.
152. Y. Lu, J. Yu, W. Ye, X. Yao, P. Zhou, H. Zhang, S. Zhao, L. Jia, Microchim. Acta 2016, 183, 2481.
153. S. Zhang, Y. Chen, Y. Huang, H. Dai, Y. Lin, Biosens. Bioelectron. 2020, 159, 112201.
154. L. Wang, L. Wu, S. Su, D. Zhu, J. Chao, L. H. Wang, Chem. Commun. 2020, 56, 12351.
155. X. Lu, G. Liu, P. Di, Y. Li, T. Xue, X. Duan, Y. Wen, Y. Zhu, Y. Cai, Q. Xu, J. Xu, Food Anal. Method 2020, 13, 2028.
156. F. Wei, X. Cui, Z. Wang, C. Dong, J. Li, X. Han, Chem. Eng. J. 2020, 408, 127240.
157. Y. Zhang, D. Li, J. Tan, Z. Chang, X. Liu, W. Ma, Y. Xu, Small 2020, 17, 2005739.

AUTHOR BIOGRAPHIES

Yan Zu received her MS degree (2009) from the Department of Chemistry at Beijing Normal University, and PhD degree (2017) from Institute of High Energy Physics, Chinese Academy of Sciences. She joined Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, Institute of High Energy Physics, Chinese Academy of Sciences in 2009. She currently focuses on the synthesis of inorganic nanomaterial for bioimaging and antibacterial and biomedical effects.

Zhanjun Gu received his BE degree (2002) from Huazhong University of Science and Technology and PhD degree (2007) from Institute of Chemistry, Chinese Academy of Science (CAS), under the direction of Prof. Jiannian Yao. He then became a postdoctoral fellow at University of Georgia. In 2009, he joined the faculty at CAS Key Lab for Biomedical Effects of Nanomaterials and Nanosafety of the Institute of High Energy Physics. His current research interests include nanomaterials synthesis, optical spectroscopy, and bioapplications of luminescent nanomaterials.

Chunying Chen received her PhD degree in Biomedical Engineering from Huazhong University of Science and Technology of China (1996). She is one of the earliest researchers in the field of nanochemistry, nano-bio interfaces, nanomedicine, environmental health effects, therapies for malignant tumors, and vaccine nanoadjuvants in China. She has made major contributions to the nanoscale biosafety and its chemical mechanism, construction of new nanomaterials, and their biomedical applications.

Lizeng Gao is currently a professor at Institute of Biophysics, Chinese Academy of Sciences (CAS). He received his PhD degree from the Institute of Biophysics, CAS in 2006. Thereafter, he worked as Postdoctoral Researcher at University of Pittsburgh, Cornell University, and University of Pennsylvania from 2006 to 2015. His research mainly...
focuses on developing novel nanozymes by mimicking structure of active center in natural enzymes. In particular, his primary goal is to design and synthesize iron-based nanozymes by mimicking the iron role and peripheral structure in the active center of natural enzymes including peroxidase, catalase, SOD, and so forth. Furthermore, with fundamental understanding on nanozymes, he tried to develop novel antimicrobial technologies and materials to combat infectious diseases.

**Wenyan Yin** received her PhD degree from Beijing Institute of Technology (2010). She is currently an associate professor at Key Lab for Biomedical Effects of Nanomaterials and Nanosafety of the Institute of High Energy Physics, Chinese Academy of Sciences (CAS).

Her research interests mainly focus on synthesis and design of intelligent nanomaterials and their applications for tumors treatment, antibacterial and biomedical effects, and biosafety.

**How to cite this article:** Zu Y., Yao H., Wang Y., et al. The age of bioinspired molybdenum-involved nanozymes: Synthesis, catalytic mechanisms, and biomedical applications. *VIEW*. 2021;2:20200188. [https://doi.org/10.1002/VIW.20200188](https://doi.org/10.1002/VIW.20200188)