

Review Article

Polyoxometalate-based nanozymes: From catalytic mechanisms toward emerging therapeutic approaches

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Abstract

Polyoxometalates (POMs) represent a rapidly evolving class of nanozymes that exhibit a range of enzyme-mimicking activities, including peroxidase-like (POD), catalase-like (CAT), superoxide dismutase-like (SOD), and oxidase-like (OXD) activities. These capabilities arise from their tunable structures, diverse compositions, and high physicochemical stability. By regulating intracellular reactive oxygen species (ROS) levels and modulating oxidative-stress processes through these catalytic activities, POMs show promise for treating various diseases. In tumor therapy, POM-based nanozymes can catalyze the generation of highly toxic ROS to induce tumor cell apoptosis. For anti-inflammatory and neuroprotective settings, their SOD-like and CAT-like activities scavenge excessive free radicals and alleviate oxidative damage. In antibacterial contexts, their POD-like and OXD-like activities enhance ROS-mediated bacterial inactivation. This versatile nanozyme class not only broadens the scope of catalytic medicine but also provides a robust materials foundation for developing efficient and precise nanotherapeutic platforms, significantly advancing the frontiers of biomedicine.

Keywords: polyoxometalate, nanozymes, therapeutic approaches, catalytic mechanisms

1. Introduction

Enzymes are core catalysts of biological processes and are indispensable in industrial manufacturing, biosensing, and biomedicine because of their high efficiency and specificity [1]. However, the broader use of natural enzymes is significantly restricted by several inherent limitations: their extraction and purification processes are complex and costly; as proteins, they are sensitive to temperature and pH, resulting in poor stability and a tendency to denature; and they are difficult to recover and reuse in reaction systems, which increases costs and the risk of product contamination [2]. To overcome these limitations, researchers have sought stable alternatives that can mimic enzymatic activity.

In this context, nanozymes, which are nanomaterials with intrinsic enzyme-like catalytic properties, have emerged as a promising alternative. Since the discovery of the POD-like activity of Fe_3O_4 nanoparticles in 2007, this field has advanced rapidly [3]. Compared to traditional enzymes, nanozymes offer several advantages: high physicochemical stability under harsh physicochemical conditions; low cost owing to straightforward synthesis and scalable production; and tunable activity that can be precisely optimized by adjusting their size, morphology, and surface chemistry [4, 5]. By leveraging these strengths, nanozymes have shown substantial potential in biomedical applications, including biosensing, antibacterial and antitumor therapies, antioxidant activity, and neuroprotection, providing innovative tools and strategies for disease diagnosis and therapy [6, 7].

Among various nanozyme platforms, metal oxides (e.g., Fe_3O_4 , CeO_2) are widely used due to their low cost and high physicochemical stability, but they typically possess polydisperse active sites and offer limited precision for tuning catalytic selectivity [8]. Metal-organic frameworks (MOFs) provide high surface areas and designable pores, yet their catalytic mechanisms can be complex and their stability under physiological conditions remains challenging [9]. In contrast, POMs, which are metal-oxo clusters of early transition metals (Mo, W, V) [10], have recently been recognized as a distinct class of nanozymes [11]. Although long studied as homogeneous catalysts [12], their

nanozyme identity was first demonstrated in the early 2010s with the discovery of intrinsic SOD-like and POD-like activities without complex surface functionalization. This positioned POMs as atomically precise nanozymes featuring well-defined structures (e.g., Keggin, Dawson, Anderson) [13–15], uniform active sites, and high tunability via metal composition adjustment or removal of specific metal-oxo units [16–18]. Notably, a single POM cluster can exhibit multiple enzyme-mimicking activities (POD, CAT, SOD, OXD) and can be further functionalized with targeting molecules or polymers to enhance biocompatibility and therapeutic specificity [19–21].

In summary, POMs constitute an ideal platform for constructing high-performance nanozymes due to their tunable composition, diverse functionalities, and long-standing history in enzyme-mimicry research [22–24]. Although their roles in catalysis and energy have been extensively explored [25–27], systematically investigating them as a distinct class of nanozymes for disease therapy represents a dynamic frontier filled with both opportunities and challenges. This review summarizes recent advances in the application of POM-based nanozymes, highlighting their multi-enzyme mimetic activities and tunable properties in treating major diseases such as bacterial infections and tumors, as well as neuroprotection. As illustrated in Fig. 1, POM nanozymes exhibit multiple enzyme-like activities, including POD, CAT, SOD, and OXD, which enable their therapeutic applications in antibacterial therapy, antitumor therapy, and neuroprotection. This review focuses on elucidating their catalytic therapeutic mechanisms, functionalization strategies, and in vitro and in vivo efficacy evaluations. Ultimately, this review aims to provide a theoretical foundation and design principles for developing next-generation therapeutic agents based on POM nanozymes.

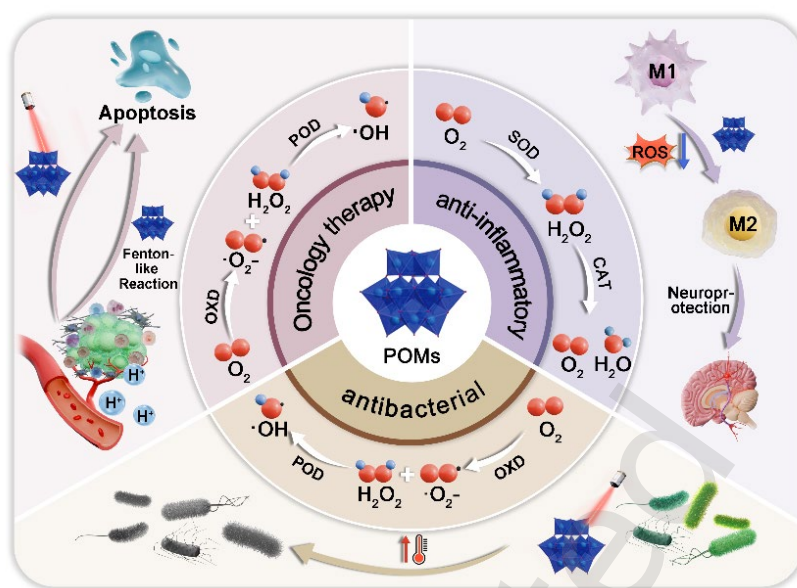


Figure 1 Schematic illustration of the multi-enzyme mimetic mechanisms of POM-based nanozymes in disease therapy.

2. Catalytic Mechanisms and Activity Modulation of POM-based Nanozymes

2.1 Principal Enzyme-Mimicking Activities and ROS Outcomes

The enzyme-mimicking functions of POM-based nanozyme systems can be organized into two opposing functional directions: ROS generation (POD-like and OXD-like) and ROS removal (SOD-like and CAT-like). This functional diversity arises from their tunable electronic structures and well-defined molecular architectures [28, 29]. The POD-like function enables a Fenton- or Fenton-like reaction in which electrons transfer from decreased metal centers (e.g., Mo^{5+} , W^{5+} , V^{4+} , Fe^{2+}) to endogenous hydrogen peroxide (H_2O_2), generating highly cytotoxic hydroxyl radicals ($\cdot\text{OH}$) that rapidly oxidize lipids, proteins, and DNA [30, 31]. This feature makes POD-like POM clusters well suited for applications requiring controlled cell killing, such as tumor ablation and bacterial inactivation. The OXD-like function directly transforms molecular oxygen (O_2) to superoxide anion (O_2^-) and H_2O_2 , which is particularly useful in creating a self-sustained H_2O_2 pool in hypoxic or nutrient-deprived microenvironments (e.g., the

tumor microenvironment). When coupled with POD-like function, OXD-like function drives a cascade process that amplifies $\cdot\text{OH}$ generation without exogenous addition of H_2O_2 [32–34].

In contrast, the ROS-scavenging mode is governed by SOD-like and CAT-like functions. SOD-like function catalyzes dismutation of O_2^- into H_2O_2 and O_2 , reducing the steady-state concentration of O_2^- and attenuating membrane lipid peroxidation [35]. CAT-like function subsequently breaks down H_2O_2 into water and molecular oxygen, preventing the formation of more damaging species (such as $\cdot\text{OH}$) via the Haber-Weiss or Fenton reaction [36–38]. Together, these functions form a two-step detoxification cascade process ($\text{O}_2^- \rightarrow \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O} + \text{O}_2$), which directly mitigates oxidative stress and underpins the anti-inflammatory and neuroprotective effects of POM nanozyme systems.

Importantly, a single POM cluster can simultaneously show both ROS-generating and ROS-scavenging functions; for example, a molybdenum-based POM can show POD-like and CAT-like functions depending on local H_2O_2 concentration, pH, and electron-donating sites. This duality can be therapeutically directed toward the desired catalytic direction by tuning POM composition (e.g., vanadium incorporation improves POD-like function) or by exploiting microenvironmental specificity (e.g., acidic pH favors POD-like reactions over CAT-like decomposition). In addition to these redox functions, certain POM structures also show hydrolase-like functions (e.g., phosphatase or protease function), enabling the hydrolysis of phosphoester bonds or peptide bonds [19, 39]. Although such functions are less central to the ROS-centric treatment approaches discussed here, they further broaden the multifunctional scope of POM nanoclusters in complex physiological contexts [7, 40]. Figure 2 schematically summarizes the principal enzyme-like functions of POM nanozyme systems and their catalytic interconversion routes among ROS.

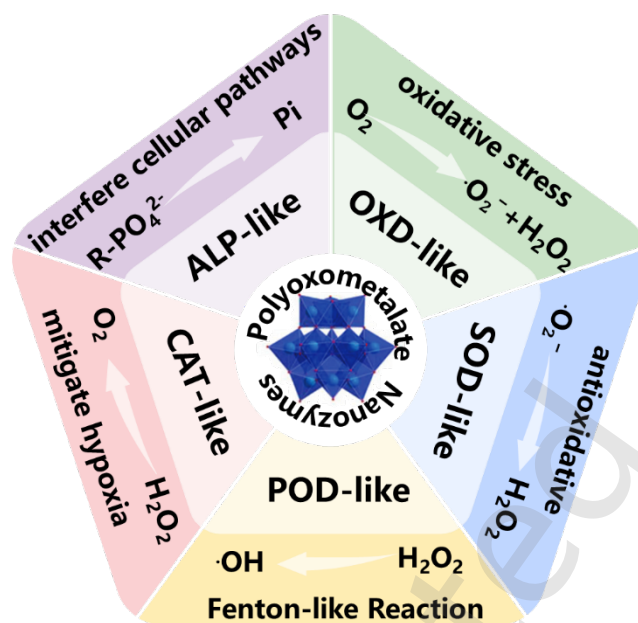


Figure 2 Schematic illustration of the multi-enzyme activities of POM-based nanozymes. The figure summarizes the major enzyme-like activities of POM nanozymes, including OXD-like, POD-like, CAT-like, and SOD-like activities, along with their catalytic products and interconversion relationships among ROS.

2.2 Strategies for Modulating Catalytic Activity

Building on the dual ROS-generating and ROS-scavenging capabilities outlined in Section 2.1, accurate control of catalytic outputs is essential for successful therapeutic translation. Despite the broad multi-enzyme functions of POM clusters characterized in buffer solutions, their catalytic performance in living systems is substantially more complex [41]. Intracellular compartmentalization, protein corona formation, substrate competition, and local pH and redox gradients can substantially alter their apparent function. Moreover, POM clusters can modulate endogenous redox-sensitive signaling routes, such as NF- κ B and MAPK cascades, by modulating upstream ROS levels [42]. Whether POM clusters can achieve biological selectivity in signaling modulation or act as nonselective redox modulators thus remains a crucial question. Given these complexities, catalytic tunability can be achieved through multi-level approaches spanning molecular design to material engineering.

At the compositional level, systematically tuning the electronic structures and coordination microenvironments of POM clusters by selecting addenda metals and introducing selective heteroatoms or dopants enables “on-demand customization” of catalytic functions [43, 44]. For example, vanadium-doped POM clusters show substantially improved POD-like function, while variations in the tungsten-molybdenum ratio can fine-tune redox potentials [45, 46].

At the material-engineering level, surface modification and hybridization approaches substantially expand functional versatility. Integrating POM clusters with smart polymers, functional proteins, or carbon-based materials not only improves their stability and biocompatibility in physiological contexts but also adds functions such as targeted recognition, stimulus responsiveness, or imaging capabilities [47, 48].

Environmental responsiveness provides another stable means of control. Many POM-based nanozyme systems show high sensitivity to local or external conditions: certain POM clusters selectively activate their POD-like function in a mildly acidic microenvironment while remaining inert at normal physiological pH; others respond to near-infrared irradiation or selective temperature changes, allowing spatiotemporal regulation of catalysis [49, 50]. Such multi-responsive characteristics enable POM-based nanozyme systems to adapt their catalytic performance to the lesion-selective microenvironment, improving treatment efficacy while reducing off-target effects on normal tissues.

To provide a systematic summary of how diverse intrinsic and extrinsic factors govern the catalytic performance of POM nanozyme systems, we summarize the principal regulatory parameters in Table 1 below.

Table 1. Key factors governing the catalytic performance of POM-based nanozyme systems

Entry	Factor	Effect on POM catalysis	Representative example/process
1	POM composition [43, 44]	Central metal selection (Mo, W, V) and heteroatom doping regulate redox potential and preferred catalytic route	V doping improves POD-like function; W-rich frameworks favor SOD/CAT-like function
2	Metal valence state [51]	Mixed-oxidation states (e.g., $\text{Mo}^{5+}/\text{Mo}^{6+}$) enable electron-transfer; the ratio shifts ROS generation versus scavenging	A higher Mo^{5+} fraction facilitates $\cdot\text{OH}$ generation
3	pH [52]	Acidic pH (5.5-6.8) facilitates POD/OXD function through protonation-accelerated Fenton chemistry; neutral pH (7.0-7.4) favors SOD/CAT function	Acidic tumor microenvironment versus near-neutral inflammatory sites
4	H_2O_2 concentration [53]	Low $[\text{H}_2\text{O}_2]$ favors POD-mediated $\cdot\text{OH}$ generation; high $[\text{H}_2\text{O}_2]$ favors CAT-mediated O_2 and H_2O generation	Self-regulating catalytic switch that limits oxidative damage
5	GSH [50]	High GSH decreases metal centers (e.g., $\text{W}^{6+} \rightarrow \text{W}^{5+}$), potentially improving POD-like function while consuming intracellular antioxidant capacity	GSH consumption amplifies oxidative stress but may gradually attenuate POM function
6	Oxygen availability [23]	OXD function requires O_2 as substrate; hypoxia limits OXD but can be partly offset by CAT-derived O_2 from endogenous H_2O_2	Hypoxic tumors may still benefit from CAT-assisted OXD supply
7	POM assembly state [54]	Monomeric, aggregated, and crystallized states differ in surface area, electron-transfer, and substrate accessibility	Acid-triggered aggregation elevates local ROS concentration
8	External stimuli [55]	NIR light accelerates electron-transfer via photothermal heating; ultrasound produces additional ROS; electric fields improve redox cycling	Temperature elevation lowers the energy barrier of Fenton-like reactions

This systematic regulatory capability, spanning molecular structure to macroscopic function, positions POM-based nanozyme systems not only as valuable model systems for studying nanozyme system catalytic processes but also as promising platforms for complex biological microenvironments. Building on these tunable catalytic processes, the following sections will discuss their treatment applications in disorder treatment.

3. Applications of POM-based Nanozymes in Oncological Therapy

3.1 Chemodynamic Therapy (CDT) Based on ROS Generation

Mechanistic bridge to oncological application. The POD-like function of POM clusters enables the Fenton or Fenton-like transformation of endogenous H_2O_2 into highly toxic $\cdot\text{OH}$, a reactive species that triggers irreversible oxidative damage to tumor cell membranes, DNA, and organelles. This Fenton-like reaction-based therapeutic approach is known as chemodynamic treatment (CDT) [56, 57]. The ROS-generating property makes POM-based nanozyme systems particularly well suited for CDT [58, 59], because the goal is to selectively elevate oxidative stress within the tumor microenvironment (TME). Critically, whether a POM cluster expresses strong POD-like function rather than competing catalase-like or superoxide dismutase-like behavior is governed by its atomic-level structure and composition. Mixed-valence molybdenum centers ($\text{Mo}^{5+}/\text{Mo}^{6+}$) act as accessible electron-donating sites that transfer electrons to H_2O_2 , and the mildly acidic TME ($\text{pH} \approx 6.5\text{-}6.8$) protonates the cluster surface and accelerates this Fenton-like reaction. Vanadium substitution ($\text{V}^{4+}/\text{V}^{5+}$) further decreases the energy barrier for $\cdot\text{OH}$ generation, thereby strengthening POD-like function. Lacunary (vacancy-containing) structures expose unsaturated metal centers that bind H_2O_2 more tightly, improving turnover efficiency. Giant wheel-shaped POM clusters such as Mo_{154} contain intervalence charge-transfer bands that absorb near-infrared irradiation, enabling photothermal enhancement of POD-like function without requiring additional photosensitizers. Moreover, the intrinsic OXD-like function of

POM clusters can self-supply H_2O_2 , while CAT-like function mitigates tumor hypoxia, both addressing the crucial metabolic limitations of the TME. Therefore, by selecting Mo-based mixed-valence clusters, vanadium- or iron-doped derivatives, lacunary frameworks, or NIR-absorbing giant POM clusters, one can rationally engineer nanozyme systems that selectively produce ROS for cancer treatment. The following sections summarize recent progress in POM-based CDT and its enhancement approaches.

Recent studies have validated this approach. For example, Hua et al. synthesized a cobalt-substituted arsenotungstate (CAW) that efficiently generates ROS to inhibit PC12 neuroblastoma cells [60]. To amplify CDT efficacy, Zhang et al. developed a supramolecular POM/polydopamine/GOx system (PCPGH) that integrates cascade glucose oxidation, H_2O_2 self-supply, GSH depletion, and photothermal ROS enhancement, synergistically inducing apoptosis and ferroptosis [61]. In a related approach, Guo et al. engineered a vanadium-capped POMOF ($[\text{Cu}_{12}(\text{Trz})_8\text{Cl}][\text{PMo}_{12}\text{O}_{40}(\text{VO})_2]$) possessing OXD, POD, and CAT activities. The cascading reactions, in which OXD-generated H_2O_2 fuels POD/CAT cycles, created a “gear-like” mechanism that amplified ROS production ($\cdot\text{OH}$, $\text{O}_2\cdot^-$, $^1\text{O}_2$) and GSH depletion. This system enabled ultra-sensitive GSH detection ($\text{LOD} = 0.062 \mu\text{M}$) and induced tumor cell apoptosis through oxidative stress and redox imbalance [62]. Similarly, Yang et al. synthesized copper-doped Mo-based POM (CP) nanoparticles with mixed valence states ($\text{Cu}^+/\text{Cu}^{2+}$, $\text{Mo}^{5+}/\text{Mo}^{6+}$), conferring simultaneous POD, CAT, and glutathione peroxidase (GPx)-like activities. Under US stimulation, CP generated ROS ($\cdot\text{OH}$, $^1\text{O}_2$) while depleted GSH, disrupting redox homeostasis and inducing ferroptosis. The system achieved a 90.5% tumor inhibition rate *in vivo*, demonstrating its strong potential for sonodynamic therapy (SDT)-enhanced CDT (Fig. 3) [51].

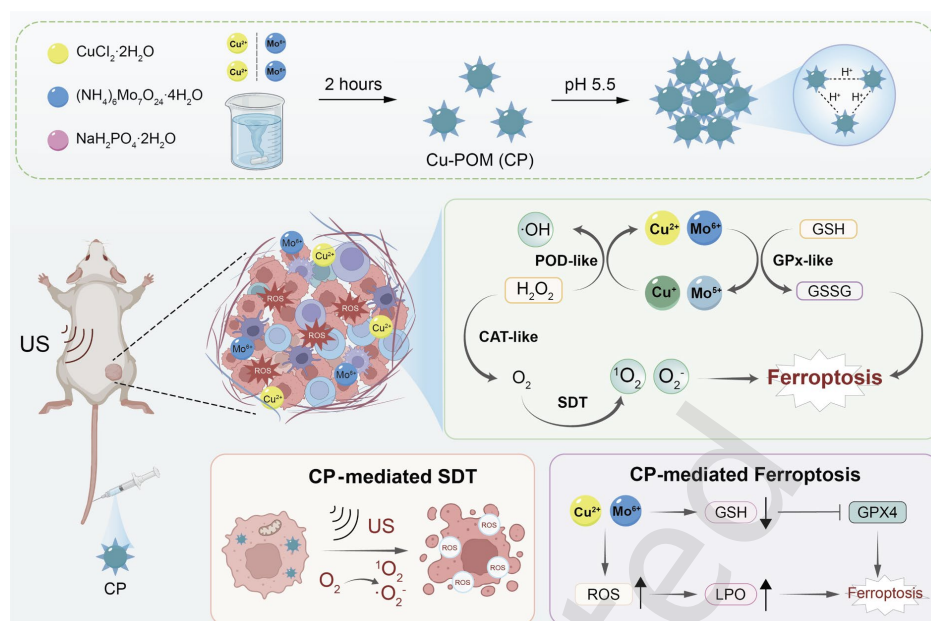


Figure 3 Schematic illustration of the preparation procedure and mechanisms of CP for synergistic therapy through enhanced sonodynamic performance and triple enzyme-mimetic catalytic activity. Reproduced with permission from Ref. [51], © Elsevier 2025.

3.2 Enhanced CDT Strategies

The therapeutic efficacy of CDT is often limited by intrinsic characteristics of the TME, such as hypoxia and low H_2O_2 availability. To address the bottleneck of insufficient endogenous H_2O_2 , POM-based nanozymes have been rationally designed to self-supply H_2O_2 via their intrinsic OXD activity or through integration with GOx cascades, while CAT activity simultaneously generates O_2 and relieves hypoxia, together overcoming the catalytic limitations in the nutrient-deprived and hypoxic TME. Accordingly, enhanced strategies have been developed to modulate the TME and integrate external energy sources.

Relieving tumor hypoxia. One key strategy leverages the CAT-like activity of POMs to relieve tumor hypoxia. For example, Wang et al. developed an oxidized molybdenum POM-copper nanocomposite (Ox-POM@Cu) that exhibits glutathione-depleting, POD-like, and CAT-like activities specifically within the TME. This system not only promotes $\cdot\text{OH}$ generation for CDT but also produces oxygen, thereby improving the

microenvironment for adjuvant therapies while enabling activatable NIR-II photoacoustic imaging for theranostic applications [63].

Integration with photothermal therapy (PTT). POM-based composites convert light into heat to accelerate catalytic reactions. Cao et al. designed a tungsten-based POM (W-POM) hydrogel paired with GOx-loaded micelles, achieving cascade glucose $\rightarrow$ $\text{H}_2\text{O}_2 \rightarrow \cdot\text{OH}$ conversion and NIR-enhanced ROS generation, with 90.5% tumor suppression, as shown in Fig. 4 [64]. In another example, Meng et al. developed PDA@POM nanospheres, in which the photothermal properties of polydopamine (PDA) synergize with the POD-like activity of W-POM. The local temperature increase under NIR irradiation accelerates the Fenton-like reaction, producing a potent combined therapeutic effect [65]. Tang et al. advanced this with POM-based nanomotors (POMotors, $\text{P}_2\text{W}_{18}\text{Fe}_4$ @PDA) that combine ROS generation with light-driven propulsion for deep tumor penetration (2-6 mm), achieving 93.86% tumor inhibition [38]. Furthermore, Miao et al. demonstrated that wheel-shaped molybdenum-based POMs (Mo_{40} and Mo_{54}) serve as effective nanozymes for synergistic cancer therapy. These clusters exhibit POD-like activity for ROS generation and induce pro-death autophagy; an effect that is significantly amplified under NIR irradiation. Mo_{40} showed superior autophagy induction and antitumor efficacy over Mo_{54} , achieving complete tumor regression *in vivo* through combined PTT/PDT/CDT. These findings highlight autophagy induction as a pivotal mechanism in POM-mediated nanotherapy [66].

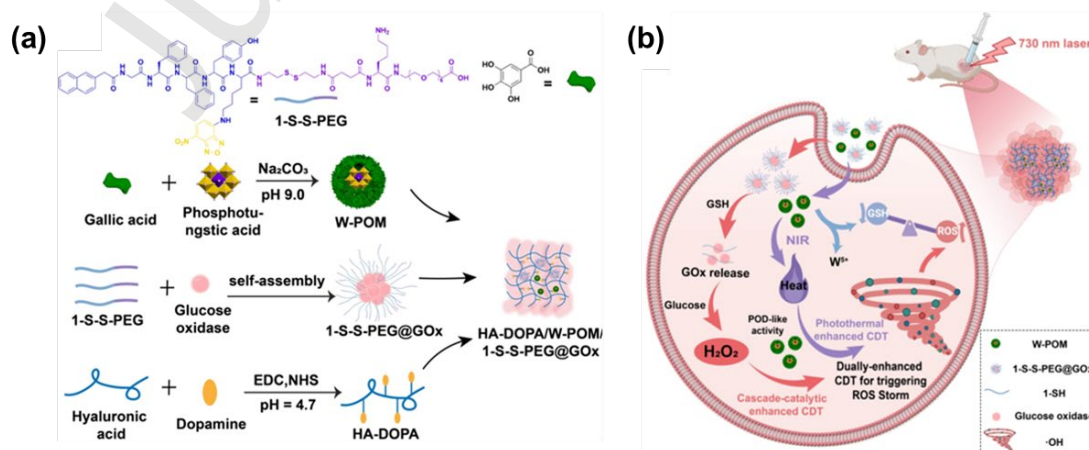


Figure 4 Schematic illustration of material synthesis and cellular mechanism;

(a) Preparation of W-POM, 1-S-S-PEG@GOx, and HA-DOPA/W-POM/1-S-S-PEG@GOx nanocomposite hydrogels. (b) Cellular mechanism by which HA-DOPA/W-POM/1-S-S-PEG@GOx induced dual-amplified ROS storm and GSH depletion in tumor cells. Reproduced with permission from Ref. [64], © American Chemical Society 2025.

Smart and structural innovations. Innovative structural designs further advance enhanced CDT. For instance, Yue et al. developed a 2D “clusterphene” structure by assembling POMs with Gox into layered nanosheets with hexagonal pores. This unique architecture, especially under external electric-field stimulation, significantly boosts POD-like activity and enables self-reinforcing catalytic/starvation therapy [67]. In addition, the concept of intelligent, responsive activation is crucial for precision therapy. This concept is exemplified by Ge et al.’s manganese-based POM single-atom enzyme (Mn-POM SAE), which undergoes a pH-triggered structural transformation in the acidic TME, switching from a nontoxic state to an active catalytic unit and enabling tumor-specific therapy. This “smart” activation unleashes multiple enzyme-like activities that disrupt redox balance and strengthen selective tumor killing [68]. Meanwhile, Wu’s group combined the giant wheel-shaped polyoxometalate Mo_{154} , which exhibits near-infrared absorption, with cationic dendron molecules to form a core-shell supramolecular composite (Fig. 5(a)). This system not only functions as an efficient photothermal agent but can also load the chemotherapeutic drug doxorubicin, enabling synergistic photothermal chemotherapy triggered by NIR laser irradiation [69]. By strategically leveraging the acidic and oxidative tumor microenvironment to enhance therapeutic specificity, Shi et al. developed an acid-aggregating Fe-POM cluster that converts H_2O_2 to $\cdot\text{OH}$, depletes GSH, and achieves complete tumor eradication under NIR-II laser without systemic toxicity (Fig. 5(b)) [70]. Together, these advances establish POM-based nanozymes as multimodal, adaptive, and intelligent therapeutic platforms, representing an important step toward precision oncology.

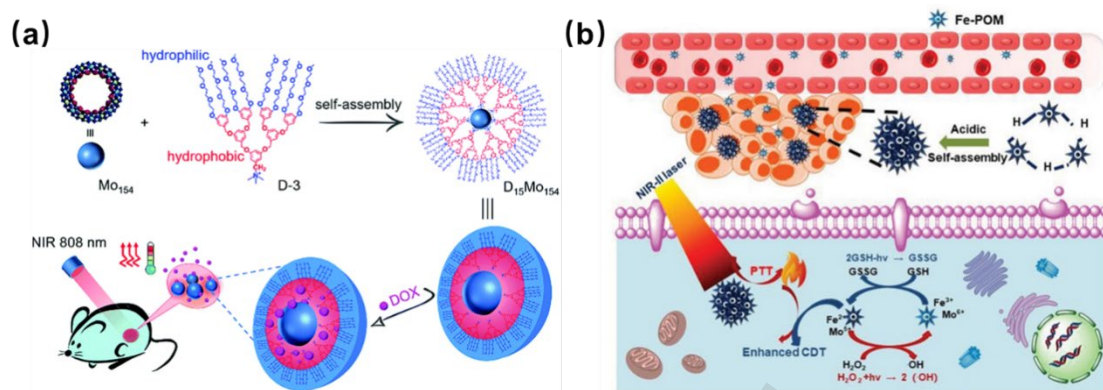


Figure 5 (a) Structural illustration of $\text{D}_{15}\text{Mo}_{154}$ complex micelles, drug loading, and laser irradiation-induced release. For clarity, the number of cationic dendrons surrounding the giant polyanionic cluster is reduced. Reproduced with permission from Ref. [69], © Royal Society of Chemistry 2018. (b) Schematic representation of Fe-POM for PTT-enhanced CDT in the NIR-II window. Reproduced with permission from Ref. [70], © Wiley 2020.

To facilitate systematic comparison of the diverse POM nanozyme systems employed in oncology treatment, Table 2 summarizes crucial parameters including POM type/composition, enzyme function, catalytic trigger, model and synergistic approach. In summary, the application of POM-based nanozymes in oncology has converged on several common strategies: leveraging POD-like activity for CDT, relieving tumor hypoxia via CAT-like activity, depleting GSH to amplify oxidative stress, and integrating photothermal or sonodynamic modalities for synergistic effects. Despite these advances, a recurring challenge remains the insufficient tumor specificity of ROS generation, which risks off-target toxicity. Moreover, most studies rely on subcutaneous tumor models, and the translation to orthotopic or metastatic settings is rarely validated. Future trends point toward stimuli-responsive POM systems (pH, redox, or enzyme-triggered) and the combination with immunotherapy or ferroptosis induction to achieve durable antitumor responses.

Table 2. Summary of POM-based nanozyme systems for oncology therapy^a

Entry	POM central/catalytic center	Composite platform (auxiliary components)	Enzyme-mimetic function	Dominant catalytic process	Disease/cell model	Synergistic approach/source
1	$\{\text{Co}_4(\text{H}_2\text{O})_2[\text{HAsW}_9\text{O}_{34}]_2\}$ [59]	CAW (Co-POM + Co-cyclen complexes)	Intrinsic ROS-generating	ROS generation	PC12 neuroblastoma cells	CDT (POM)
2	Mo-POM [60]	PCPGH (Mo-POM/polydopamine/Gox supramolecular)	POD	H_2O_2 supply + GSH consumption + ROS generation	4T1 cells	CDT (POM), PTT (PDA)
3	$\{\text{H}_3\text{PMo}_{12}\text{O}_{40}\}$ [61]	POMOF $([\text{Cu}_{12}(\text{Trz})_8\text{Cl}][\text{PMo}_{12}\text{O}_{40}(\text{VO})_2])$	OXD, POD, CAT	GSH consumption + ROS generation	melanoma cells	CDT (POM)
4	Mo-POM [62]	CP (Mo-POM + CuCl_2)	POD, CAT, GPx	GSH consumption + ROS generation	4T1 cells	SDT (US), CDT (POM), ferroptosis (POM)
5	Mo-POM [63]	Ox-POM@Cu (Mo-POM + CuCl_2)	POD, CAT	GSH consumption + ROS generation	4T1 cells	PTT (Cu), CDT (POM)
6	$\{\text{H}_3\text{PW}_{12}\text{O}_{40}\}$ [64]	HA-DOPA/W-POM/1-S-S-PEG@GOx	POD	H_2O_2 supply + ROS generation	A375 cells	PTT (POM), CDT (POM)
7	W-POM [65]	PDA@POM (PDA + W-POM)	POD	H_2O_2 supply + ROS generation	HeLa cells	PTT (PDA), CDT (POM)
8	$\{\text{P}_2\text{W}_{18}\text{Fe}_4\}$ [38]	POMotors ($\text{P}_2\text{W}_{18}\text{Fe}_4$ @PDA)	POD	H_2O_2 supply + ROS generation	HeLa cells	PTT (PDA + POM), CDT (POM)
9	$\{\text{Mo}_{40}\}/\{\text{Mo}_{54}\}$ [66]	—	POD	H_2O_2 supply + ROS generation	A549 cells	PTT/PDT (POM), CDT (POM), autophagy (POM)

				H ₂ O ₂ elevate + ROS generation + GSH consumption		Electric-field- improved CDT (POM)
10	{NdPW ₁₁ } [67]	POMG (NdPW ₁₁ + Gox)	POD, CAT, GPx		HeLa cells	
11	{MnPW ₁₁ } [68]	Mn-POM single-atom enzyme	POD, OXD, CAT, GPx	H ₂ O ₂ elevate + ROS generation + GSH consumption	HeLa cells	CDT (POM)
12	{Mo ₁₅₄ } [69]	D ₁₅ Mo ₁₅₄ @DOX (Mo ₁₅₄ + cationic dendron + DOX)	POD	ROS generation	QSG-7701 cells	POM- mediated PTT/CDT plus DOX chemotherapy
13	Fe-POM [70]	—	POD	H ₂ O ₂ elevate + ROS generation + GSH consumption	HeLa cells	PTT (POM), CDT (POM)

^aPEG = polyethylene glycol, PDA = polydopamine, DOX = doxorubicin. "—" indicates that it is not a composite platform. 4T1 cells = mouse breast cancer cells, A375 cells = human malignant melanoma cells, A549 cells = human non-small cell lung cancer cells, QSG-7701 cells = human hepatocyte cells.

4. ROS-Scavenging Therapy for Antioxidant and Cytoprotective Applications (SOD/CAT-like Dominated)

4.1 Oxidative Stress as a Common Pathological Driver

ROS play a profoundly dualistic role in the inflammatory process, functioning as a critical double-edged sword [71]. In their beneficial capacity, ROS act as essential intracellular signaling molecules that help orchestrate a coordinated immune response. When produced in a controlled and regulated manner by activated immune cells, ROS function as secondary messengers within intracellular signaling pathways, facilitating

the initiation and coordination of inflammation. Specifically, they activate key pro-inflammatory cascades, including the NF- κ B and MAPK pathways [72]. This activation upregulates the expression of genes encoding cytokines, chemokines, and adhesion molecules, which collectively promote the recruitment of additional immune cells to sites of threat and amplify defensive responses necessary for effective pathogen clearance and tissue repair [73]. However, when ROS generation becomes excessive and overwhelms cellular antioxidant defenses, oxidative stress ensues, shifting their role from signaling mediators to damaging agents. In this pathological context, ROS induce widespread injury to fundamental cellular structures. They promote lipid peroxidation of cell membranes, cause oxidative modifications of proteins, rendering them dysfunctional, and induce DNA strand breaks. This direct damage compromises cellular integrity and function and perpetuates a vicious cycle of inflammation. The release of intracellular components acting as damage-associated molecular patterns (DAMPs) further amplifies the inflammatory cascade, promoting chronic inflammatory disease progression and tissue destruction [74]. The well-established duality of ROS underscores the crucial need of precisely modulating their levels for therapeutic benefit. In physiological contexts, low ROS levels serve as essential signaling molecules that should be preserved rather than indiscriminately eliminated. However, in diverse disorder conditions such as chronic inflammation, ischemia - reperfusion injury, neurodegenerative disorders, colitis, and diabetic wounds, ROS are overproduced that exceed endogenous antioxidant defenses, leading to tissue damage and disorder development. In these contexts, rather than a blanket inhibition of all ROS, selectively removing excessive ROS to reestablish redox balance represents a unified cytoprotective approach. Accordingly, POM-based nanozyme systems with SOD-like and CAT-like functions are well suited for this purpose, as they catalytically eliminate superoxide and hydrogen peroxide without fully abolishing all ROS signaling.

4.2 Antioxidant Mechanisms: SOD-like and CAT-like Cascade

Unlike cancer treatment where ROS generation is desired, the treatment of oxidative

stress-driven disorders, including rheumatoid arthritis, Alzheimer's disorder, intracerebral hemorrhage, inflammatory bowel disorder, diabetic wounds, and bone defects, requires effective ROS clearance [75]. Here, the dual superoxide dismutase-like and CAT-like functions of POM nanozyme systems become therapeutically important. Specifically, SOD-like function catalyzes dismutation of O_2^- into H_2O_2 and oxygen, while CAT-like function subsequently breaks down the produced H_2O_2 into water and oxygen [25]. This cascade process ROS-scavenging process directly mitigates oxidative stress, perturbs the inflammatory positive-feedback loop in which excessive ROS sustain inflammatory signaling, and facilitates resolution of inflammation [26, 76].

The preferential manifestation of these scavenging functions over peroxidase-like function is governed by selective structural features of the POM cluster. Molybdenum-based POM clusters with mixed Mo^{5+}/Mo^{6+} valences function optimally near neutral pH (7.0-7.4), where electron-transfer kinetics for O_2^- dismutation exceeds that for H_2O_2 reduction, favoring SOD/CAT over POD. Tungsten-based POM clusters possess lower redox potentials and tend to preserve ROS-scavenging function even at mildly acidic inflammatory sites, and their ultrasmall derivatives with diameters of 1 to 5 nanometers show improved renal clearance and decreased protein corona formation, preserving surface availability for ROS removal *in vivo*. Lacunary polyoxometalates that contain vacant sites expose terminal oxo ligands which selectively bind and stabilize superoxide intermediates, enhancing SOD-like turnover. Avoiding redox-active dopants such as vanadium or iron suppresses undesirable Fenton-like side reactions, ensuring the cluster functions predominantly as an antioxidant. By sequentially eliminating ROS through this cascade process, POM-based nanozyme systems substantially decrease the total oxidative-stress burden and alleviate oxidative damage. The following examples illustrate how POM nanozyme systems that follow these structural principles treat rheumatoid arthritis, osteoarthritis, cerebral ischemia, Alzheimer's disorder, inflammatory bowel disorder, and diabetic wounds.

4.3 Application Examples in Antioxidant and Cytoprotective Therapy

The therapeutic potential of POM-based nanozyme systems has been showed in multiple oxidative stress-driven disorders. Below, we organize representative examples by disorder category, highlighting the shared cytoprotective process of ROS removal.

Rheumatoid arthritis and osteoarthritis. In these inflammatory joint disorders, excessive ROS perpetuate synovial inflammation and cartilage degradation. POM nanozymes with dual SOD/CAT activities scavenge ROS via $\text{Mo}^{5+}/\text{Mo}^{6+}$ redox cycling. Shi and colleagues showed that NIR-responsive Mo-POM nanoclusters disrupt the inflammatory positive feedback loop in OA models, attenuating cartilage degradation without systemic toxicity [77]. Yang et al. developed a supramolecular platform (PCSN@MTX) that combines ultrasound-enhanced ROS scavenging, oxygen generation, and on-demand methotrexate release, promoting M1-to-M2 macrophage polarization and alleviating joint damage in collagen-induced arthritis (Fig. 6) [78].

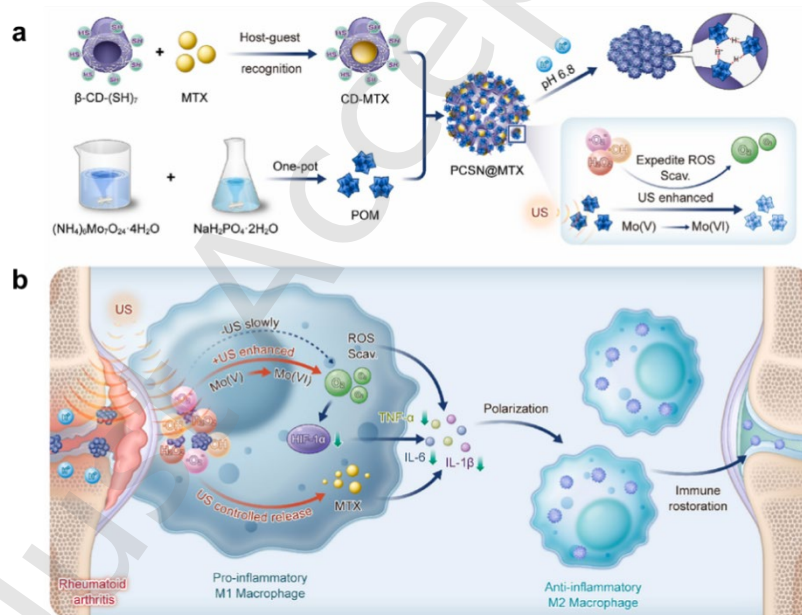


Figure 6 Schematic illustration of the supramolecular nanoplatforms PCSN@MTX, that modulates M1-like macrophage polarization through US-enhanced ROS scavenging and in situ oxygen production to treat rheumatoid arthritis (RA). (a) Schematic of the fabrication of PCSN@MTX and the US-enhanced ROS catalytic mechanism. (b) Following intravenous administration, PCSN@MTX efficiently accumulates in hyperplastic inflamed synovium due to edema and neovascularization. In response to the acidic microenvironment, PCSN@MTX aggregates and eliminates ROS while generating O_2 . Notably, its

catalytic activity can be further enhanced by US irradiation. The combination of MTX release and ROS scavenging synergistically promotes the polarization of M1-like macrophages into M2-like macrophages, thereby alleviating chronic inflammation and mitigating joint damage. Reproduced with permission from Ref. [78], © Elsevier Science Ltd.2025.

Diabetic bone regeneration and wound healing. Hyperglycemia-induced oxidative stress impairs bone repair and delays wound closure. Liao et al. used an injectable GelMA/POM hydrogel to scavenge ROS, upregulate osteogenic markers (BMP2, RUNX2), and activate PI3K/Akt signaling, thereby improving diabetic bone regeneration [79]. Our group recently provided a more comprehensive demonstration of POM-mediated immunomodulation in bone defect repair. We developed an injectable Mo-POM@GG/nHA hydrogel that scavenges H_2O_2 , O_2^- , and $\cdot\text{OH}$ through reversible $\text{Mo}^{5+}/\text{Mo}^{6+}$ cycling. Transcriptomic and proteomic analyses revealed that Mo-POM nanoclusters suppress the MAPK pathway (ERK, JNK, p38), reduce IL-1 β expression, and promote M2 macrophage polarization (CD206, IL-4, IL-10). In a mouse calvarial defect model, the hydrogel significantly lowered pro-inflammatory cytokines and enhanced new bone formation (micro-CT and histology). This work provides the first evidence that POM-based nanozymes can achieve pathway-selective anti-inflammatory effects through omics-guided analysis, bridging in vitro catalysis with in vivo signaling modulation [42]. For diabetic wounds, Pu et al. fabricated a zinc-based polyoxometalate nanozyme system-functionalized hydrogel (AHAMA/CS-GOx@Zn-POM) that combines glucose consumption, ROS removal, and zinc ion release to remodel the hyperglycemic-immune microenvironment and facilitate healing (Fig. 7) [80].

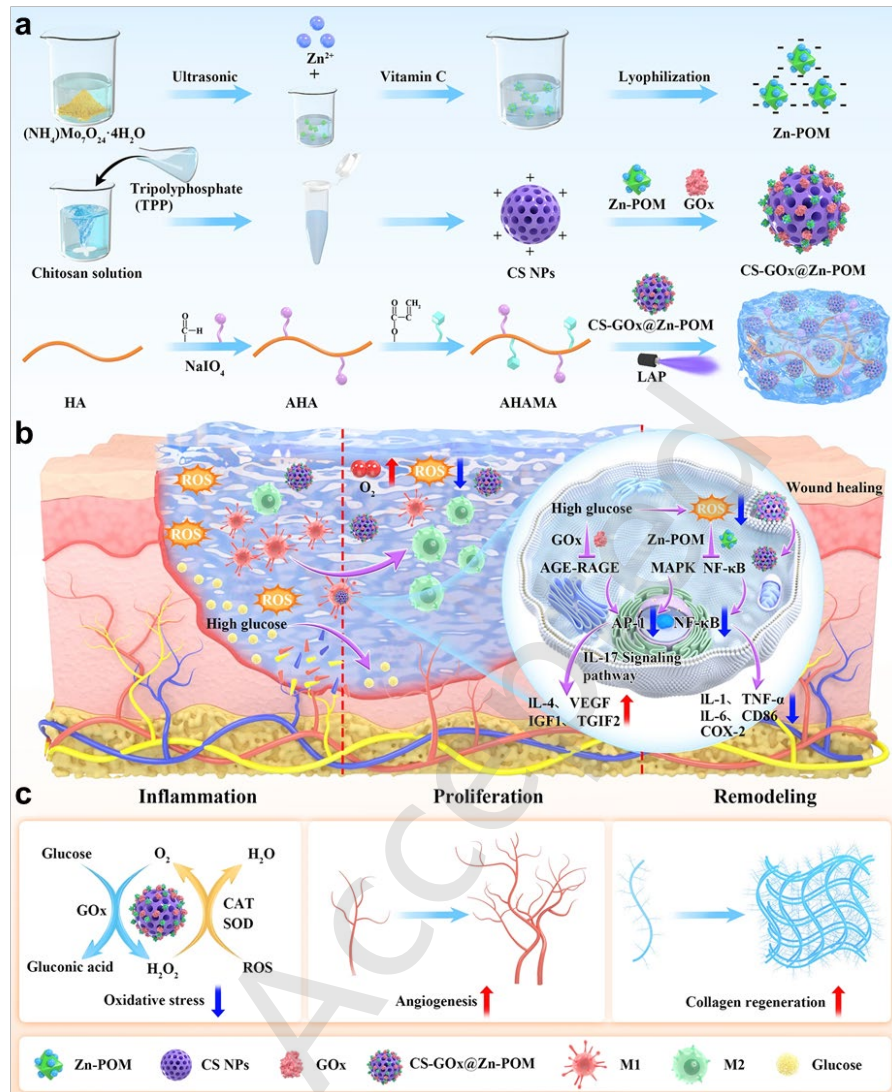


Figure 7 Illustration of the nanozyme-functionalized hydrogel for the treatment of diabetic wounds. (a) Preparation process of the nanozyme functionalized hydrogel. (b) Mechanism by which the nanozyme-functionalized hydrogel promotes diabetic wound healing and Zn-POM regulates macrophage polarization. (c) Cascade reactions through which the hydrogel facilitates glucose consumption, ROS scavenging, angiogenesis, and collagen regeneration. Reproduced with permission from Ref. [80], ©BMS 2024.

Cerebral ischemia/reperfusion injury and intracerebral hemorrhage. Acute brain injuries involve burst ROS generation that leads to neuronal apoptosis and neurological deficits. Li and colleagues showed the neuroprotective efficacy of molybdenum-based POM nanoclusters in a rat model of cerebral I/R injury. The POM nanoclusters

efficiently removed multiple ROS via reversible $\text{Mo}^{5+}/\text{Mo}^{6+}$ redox cycling, reducing oxidative stress and membrane lipid peroxidation, suppressing neuronal apoptosis, and reducing pro-inflammatory cytokines ($\text{TNF-}\alpha$ and IL-6) [81]. Xu et al. prepared neutrophil-like cell membrane-coated molybdenum-based nanoclusters (POM@Mem) for targeted neuroprotection after intracerebral hemorrhage. The POM central provides intrinsic SOD and CAT-like functions, while the neutrophil membrane enables accurate targeting to hemorrhage sites [82]. Additionally, to address inflammation commonly associated with conventional photothermal treatment, Zha and Sun's team prepared ultrasmall tungsten-based polyoxometalate nanoclusters (W-POM NCs) inspired by the Folin-Ciocalteu assay. These nanoclusters show both photothermal properties and efficient ROS removal via $\text{W}^{5+}/\text{W}^{6+}$ redox cycling, while their ultrasmall size enables rapid renal clearance, improving safety and biocompatibility (Fig. 8) [83].

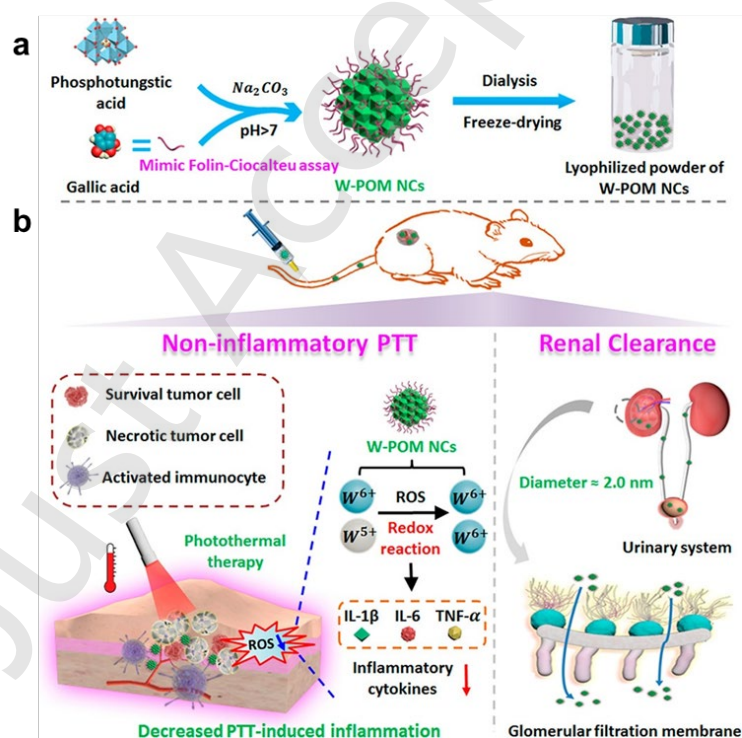


Figure 8 Schematic illustration of (a) the synthesis and (b) the underlying mechanisms of W-POM NCs for non-inflammatory PTT with rapid renal clearance. Reproduced with permission from Ref. [83], © Amer Chemical Soc 2020.

Inflammatory bowel disorder (IBD). Oxidative stress in the colonic mucosa drives

chronic inflammation and tissue damage. Wang et al. prepared tungsten-based POM nanoclusters (W-POM NCs) as an orally administered therapeutic agent for IBD. These nanoclusters show broad-spectrum ROS removal via mixed-valence W^{5+}/W^{6+} states and allow non-invasive CT tracking. In DSS-triggered colitis models, W-POM NCs mitigated disorder severity, decreased pro-inflammatory cytokines, and reestablished colonic microstructure without systemic toxicity (Fig. 9) [84].

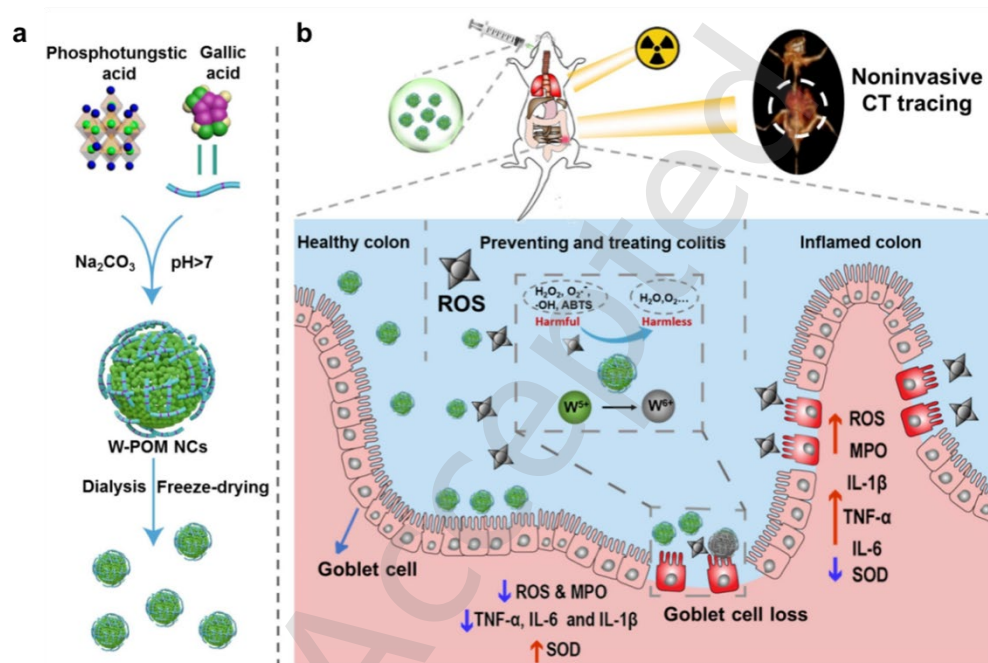


Figure 9 Schematic diagram of (a) W-POM NCs preparation and (b) the underlying mechanism of CT-traceable mitigation of colonic inflammation. Reproduced with permission from Ref. [84], © Elsevier 2021.

Alzheimer's disorder (AD). AD pathology involves amyloid- β toxicity, metal dyshomeostasis, and chronic neuroinflammation, all linked to oxidative stress. CeONP@POM clusters efficiently degrade A β monomers and fibrils through hydrolytic cleavage while simultaneously scavenging excess ROS via intrinsic SOD-mimetic function. This nanozyme system can cross the blood-brain barrier and regulate microglial activation, alleviating oxidative stress and neuronal injury [36]. Similarly, AuNPs@POMD-8pep combines protease-like function for A β degradation, SOD-mimetic capacity for ROS clearance, and metal-chelating ability to perturb Cu-triggered A β aggregation, representing a multifunctional antioxidant/cytoprotective

platform (Fig. 10) [47].

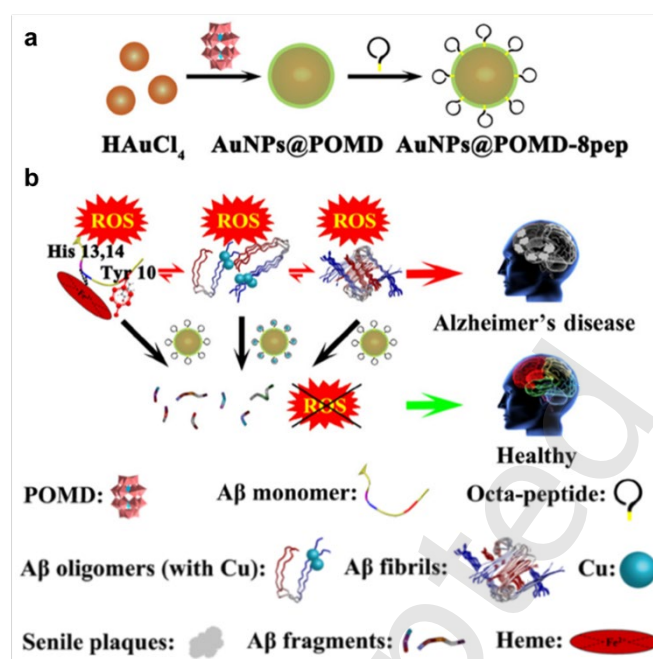


Figure 10 Aβ pathways influenced by AuNPs@POMD-8pep. (a) Synthetic route of the nanozyme. (b) AuNPs@POMD-8pep as a multifunctional nanozyme modulating multiple facets of Alzheimer's disease. Reproduced with permission from Ref. [47], © Tsinghua University Press 2016.

A systematic summary of POM-based nanozyme systems applied in antioxidant and cytoprotective treatment is provided in Table 3, which includes disorder model, POM composition, enzyme function, synergistic approach, and biosafety information. Overall, the anti-inflammatory applications of POM-based nanozymes share a unifying mechanism: the dual SOD- and CAT-mimetic activities that convert superoxide and H_2O_2 into harmless products, thereby breaking the vicious cycle of oxidative stress and chronic inflammation. A notable trend is the evolution from simple ROS scavenging to active immunomodulation, particularly the polarization of macrophages from pro-inflammatory M1 to pro-healing M2 phenotypes. However, key unresolved challenges include the limited ability of most POMs to cross the blood-brain barrier for neurodegenerative diseases (despite some modified systems), and the lack of long-term safety data in chronic inflammatory conditions such as rheumatoid arthritis or inflammatory bowel disease. Future efforts should prioritize disease-targeted delivery (e.g., using cell-membrane coating or responsive hydrogels) and combination with

conventional anti-inflammatory drugs to reduce systemic side effects.

Table 3. Summary of POM based nanozyme systems for antioxidant and cytoprotective therapy^a

Entry	POM central/catalytic center	Composite platform/auxiliary components	Enzyme mimetic function	Dominant catalytic process	Disease/cell model	Synergistic approach/source	Biosafety
1	Mo-POM [77]	—	SOD, CAT	Mo ⁵⁺ /Mo ⁶⁺ redox cycling → O ₂ ^{•-} → H ₂ O ₂ → H ₂ O + O ₂	OA	PTT (POM)	superior biocompatibility
2	Mo-POM [78]	PCSN@MTX (β-CD + MTX + Mo-POM)	SOD, CAT	Scavenging ROS + O ₂ generation → decrease HIF-1α	CIA	US (β-CD + MTX + Mo-POM)	No cytotoxic
3	Mo-POM [79]	GelMA/PO M hydrogel	SOD, CAT	Scavenging ROS → upregulate BMP2, RUNX2 ; PI3K/Akt	Bone defects in DM	—	Good biocompatibility
4	Mo-POM [42]	Mo-POM@GG/nHA hydrogel	SOD, CAT	Mo ⁵⁺ /Mo ⁶⁺ redox cycling →	Calvarial bone defect	—	No significant toxicity (0-500 µg/mL)

				remove ROS; inhibit MAPK route			
				Glucose consumption + ROS removal + Zn ²⁺			
5	Zn-POM [80]	AHAMA/C S-GOx@Zn- POM hydrogel	SOD, CAT	release → suppress ing the MAPK/I L-17 signalin g Mo ⁵⁺ /M o ⁶⁺	Diabetic wound	—	No significant toxicity (0- 200 µg/mL)
6	Mo-POM [81]	—	SOD, CAT	redox cycling → remove ROS	Cerebral I/R injury	—	low toxicity
7	Mo-POM [82]	POM@Mem (neutrophil membrane-coated)	SOD, CAT	Targeted ROS removal	ICH	Neutrophil membrane targeting	low toxicity
8	W-POM [83]	W-POM NCs (W- POM + gallic acid)	SOD, CAT	Mo ⁵⁺ /M o ⁶⁺ redox cycling → remove ROS	Inflamm atory response s caused by PTT	—	Cell viability > 93.4 ± 7.6%
9	W-POM	W-POM	SOD,	Broad-	IBD	—	Nontoxicity

	[84]	NCs (W-POM + gallic acid)	CAT	spectrum ROS removal			
10	K ₈ [P ₂ CoW ₁₇ O ₆₁] [36]	CeONP@-POM clusters (CeO ₂ nanoparticle s + POM)	SOD	Hydrolytic A β degradation + ROS removal	AD	—	Prominent Good biocompatibility
11	Wells-Dawson structure POM [47]	AuNPs@PO MD-8pep (Au nanoparticle s + POM + N-Ac-Cys-heptapeptide complex)	SOD	A β degradation + metal chelation + ROS clearance	AD	Protease functions + SOD-like functionality (POM) + metal-ion chelation capabilities (A β oligomers with Cu)	Low cytotoxicity

^a β -CD = β -cyclodextrin, MTX = methotrexate, CIA = collagen-triggered arthritis, DM = diabetes mellitus, GG = gellan gum, nHA = nano-hydroxyapatite, AHAMA = methacrylic anhydride-modified hyaluronic acid hydrogel, CS = chitosan, I/R = ischemia/reperfusion, ICH = intracerebral hemorrhage, IBD = inflammatory bowel disorder. "—" indicates that it is not reported in the cited references.

5. ROS-Burst Therapy for Bacterial and Biofilm Eradication (POD/OXD-like Dominated)

5.1 ROS-Based Antibacterial Mechanisms

Bacterial infections, particularly those involving biofilms in chronic wounds, require strong and broad-spectrum bactericidal action. The peroxidase-like and oxidase-like functions of POM nanozyme systems leverage the distinctive redox properties of their multivalent metal sites, such as Mo⁵⁺/Mo⁶⁺ and W⁵⁺/W⁶⁺, to produce an intense burst of reactive oxygen species. These functions function through a catalytic cascade process: oxidase-like function first transforms dissolved oxygen into O₂^{•−} and H₂O₂,

which are then rapidly processed by peroxidase-like function through rapid electron-transfer between metal-oxidation states, generating a localized burst of highly reactive $\cdot\text{OH}$ [85].

The structural determinants for amplifying this ROS burst in the biofilm microenvironment, which is mildly acidic with pH of approximately 5.5 to 6.0 and enriched in H_2O_2 because of bacterial metabolism, are distinctive from those for tumor treatment. Vanadium or iron doping substantially lowers the energy barrier for $\cdot\text{OH}$ generation, as observed in vanadium-substituted and iron-doped POM clusters where the $\text{V}^{4+}/\text{V}^{5+}$ or $\text{Fe}^{2+}/\text{Fe}^{3+}$ couples promote electron-transfer. Mixed-valence $\text{W}^{5+}/\text{W}^{6+}$ centers in POM clusters show pH-responsive aggregation, concentrating the nanozyme system within biofilms while improving electron-transfer to H_2O_2 . Heterojunction construction that couples POM clusters with semiconductors such as WS_2 creates a photoinduced electron-accepting sink that continuously restores decreased metal centers, sustaining $\cdot\text{OH}$ generation under near-infrared irradiation. Covalent conjugation with cationic polymers and peptides not only improves bacterial-membrane penetration but also creates localized catalytic pockets that increase local ROS concentration. Importantly, the acidic and H_2O_2 -rich biofilm microenvironment naturally improves this catalytic performance, and the self-assembly tendency of certain POM structures under acidic conditions further facilitates local accumulation and antibacterial potency [49].

The produced hydroxyl radicals initiate a strong, non-selective attack on bacterial pathogens. They trigger membrane lipid peroxidation, irreversibly disrupting bacterial cell membranes and causing cytoplasmic leakage. Simultaneously, they oxidatively damage intracellular proteins and enzymes and trigger genomic DNA strand breaks. This multifaceted oxidative assault is highly efficient against recalcitrant biofilms, as the small and diffusible hydroxyl radicals can penetrate the extracellular polymeric substance that often protects bacteria from conventional antibiotics. Continuous catalytic generation of radicals not only kills surface bacteria but also gradually degrades the extracellular polymeric substance matrix, perturbing biofilm architecture and eliminating embedded cells [86]. Unlike conventional antibiotics that target

selective metabolic routes, this ROS-based physicochemical attack is less likely to induce resistance, positioning POM nanozyme systems as a stable broad-spectrum approach for overcoming antibiotic resistance in chronically infected wounds [87, 88]. The following subsections describe photocatalytic, responsive, and biofilm-targeting approaches derived from these structural designs.

5.2 Specific Antibacterial Strategies

Photocatalytic antibacterial therapy. Leveraging their intrinsic enzyme-like functions, POM nanozymes enable spatially controlled antimicrobial action through photocatalysis. The semiconductor-like properties of POMs allow specific-wavelength irradiation to generate electron-hole pairs. These photogenerated charge carriers then mediate redox reactions with surrounding molecules, such as water or oxygen, leading to marked light-triggered amplification of ROS production. This mechanism provides a spatiotemporally controlled antibacterial effect, as the potent ROS burst is activated only upon localized irradiation at the infection site. By combining this photocatalytic function with their inherent biocatalytic properties, POM-based nanozymes offer a refined and targeted platform for managing localized infections.

By leveraging the unique redox activity of POMs and the photocatalytic properties of WS₂, Lv et al. developed a heterojunction nanocomposite, **GdP₅W₃₀@WS₂**, for NIR-enhanced treatment of infected wounds (Fig. 11). Under 808 nm laser irradiation, photoexcited electrons from WS₂ promote the reduction of W⁶⁺ to W⁵⁺ active sites in **GdP₅W₃₀**, enabling continuous ·OH generation via a Fenton-like reaction and amplifying CDT. The nanocomposite also depletes GSH through redox cycling, disrupting the bacterial antioxidant system and further enhancing ROS-mediated antibacterial efficacy. Combined with its acidic microenvironment-enhanced photothermal performance, **GdP₅W₃₀@WS₂** achieves synergistic CDT/PTT, effectively eradicating biofilms and accelerating wound healing *in vivo* without systemic toxicity. This study demonstrates a smart photocatalytic strategy for using redox-heterojunction nanomaterials to treat resistant bacterial infections [89].

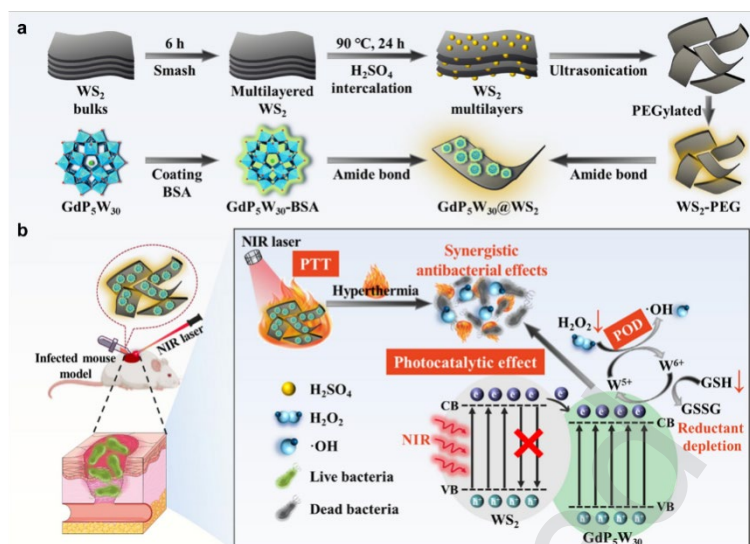


Figure 11 (a) Schematic illustration of the synthesis procedure for the heterojunction $\text{GdP}_5\text{W}_{30}@WS_2$. (b) Synergistic antibacterial mechanism of photocatalytic ally enhanced POD-like catalytic activity via rapid W^{6+}/W^{5+} redox cycling and PTT based on the $\text{GdP}_5\text{W}_{30}@WS_2$ heterojunction under NIR laser irradiation. Reproduced with permission from Ref. [89], © Elsevier Science Ltd.2023.

Building on the heterojunction strategy for enhanced catalytic cycling, another intelligent polyoxometalate-cluster system has been developed to target the biofilm microenvironment through dual environmental responsiveness. Zhang et al. constructed a bacteria-responsive antimicrobial platform using tungsten-based polyoxometalate nanoclusters ($\text{GdW}_{10}\text{O}_{36}$ NCs) to modulate the biofilm microenvironment and promote infected wound healing (Fig. 12). These nanoclusters exhibit dual responsiveness to acidity and reductive conditions: in acidic biofilm microenvironments, protonation induces self-assembly into aggregates, thereby promoting accumulation within biofilms and improving NIR photothermal conversion. Under reductive conditions, reducing agents such as glutathione convert W^{6+} to W^{5+} , significantly boosting NIR absorption and photothermal performance. The reduced nanoclusters simultaneously show strong POD-like activity, catalyzing endogenous low-concentration H_2O_2 to generate $\cdot OH$ for CDT. NIR laser irradiation further synergistically amplifies both photothermal effects and enzymatic catalytic activity, resulting in efficient biofilm eradication and bacterial

killing. *In vitro* and *in vivo* studies demonstrate that this platform effectively inhibits biofilm formation by Gram-negative *Escherichia coli* (*E. coli*) and Gram-positive *Staphylococcus aureus* (*S. aureus*), while accelerating infected wound healing with excellent biocompatibility. This study provides a new strategy for designing smart, responsive antibacterial nanomaterials for biofilm-associated infections [90].

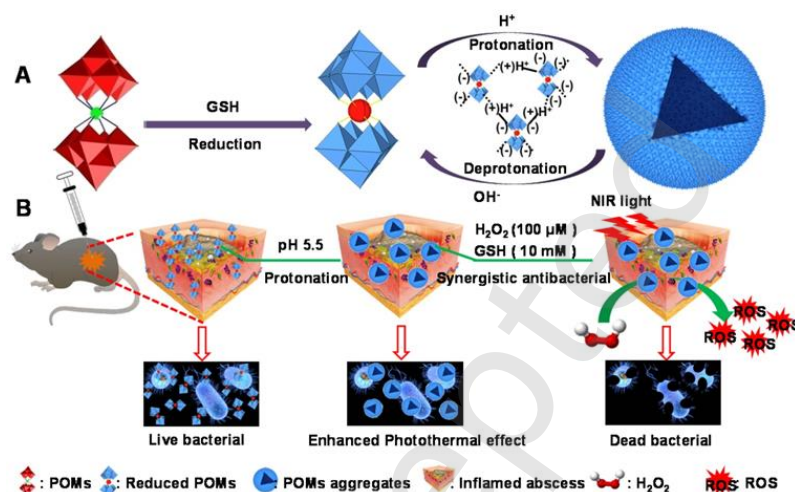


Figure 12 Schematic illustration of pH/GSH responsiveness of $\text{GdW}_{10}\text{O}_{36}$ NCs, illustrating their combined POD-like catalytic and photothermal effects to regulate BMEs, enhance antibiofilm activity, and promote wound healing. Reproduced with permission from Ref. [90], © Ivyspring International Publisher 2020.

Based on the unique redox activity and environmental responsiveness of POMs, Liu et al. developed a chronologically adaptive hydrogel, Fe-POM@HA, for treating diabetic chronic wounds (Fig. 13). By integrating Fe-doped reduced molybdenum-based polyoxometalate clusters into a hyaluronic acid matrix, the hydrogel exhibits stage-specific functions synchronized with the dynamic wound healing process. During the acidic bacterial infection phase, Fe-POM self-aggregates within biofilms and catalyzes endogenous H_2O_2 to generate ROS, while synergistically enhancing NIR-II photothermal conversion in a pH- and GSH-responsive manner. This dual activation promotes bacterial ferroptosis by inducing lipid peroxidation and suppressing GPX4 activity. As the wound progresses to a neutral inflammatory environment, mixed-valence Fe-POM clusters act as a broad-spectrum antioxidant, neutralizing excess ROS

and RNS while continuously replenishing O_2 and cycling H_2O_2 to alleviate oxidative stress and hypoxia. In the proliferation phase, the hydrogel modulates macrophage polarization toward the M2 phenotype, downregulates pro-inflammatory cytokines, and enhances angiogenesis and collagen deposition, thereby accelerating tissue regeneration. *In vivo* studies using MRSA-infected diabetic rat models confirm that Fe-POM@HA, particularly under NIR-II irradiation, markedly promotes wound closure, reduces inflammation, and restores skin structure without systemic toxicity. This work presents a smart, multi-stage adaptive hydrogel platform that incorporates antibacterial, antioxidant, immunomodulatory, and pro-healing functions for comprehensive diabetic wound therapy [91].

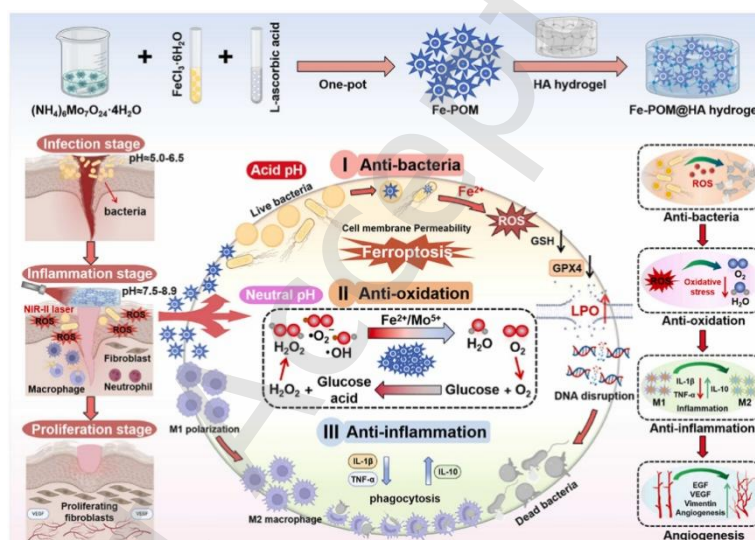


Figure 13 Fe-POM@HA hydrogel for diabetic wound therapy. Schematic of Fe-POM@HA hydrogel synthesis and its mechanisms of action, including the induction of bacterial ferroptosis in the acidic microenvironment and antioxidant-mediated immunomodulation during diabetic wound healing in a neutral environment. Reproduced with permission from Ref. [91], © Elsevier Science Ltd.2024.

ROS-based biofilm disruption strategies using POM nanozymes. While photocatalytic approaches show promising antibacterial activity through ROS generation, their efficacy against highly resilient biofilms remains limited. POM-based nanozymes overcome this challenge by harnessing their potent ROS-generating capability to achieve exceptional efficacy against established bacterial biofilms.

Effective biofilm eradication requires not only potent bactericidal agents but also the ability to penetrate and dismantle the protective EPS matrix [92, 93]. Composed of polysaccharides, proteins, and extracellular DNA, this matrix acts as a formidable barrier that traps antimicrobials and shelters resident bacteria [94, 95]. POM nanozymes address this dual challenge through a spatially targeted, catalytic attack: the $\cdot\text{OH}$ and other ROS generated via their POD/OXD-mimetic cascades are highly reactive yet short-lived [71]. This property, rather than being a limitation, becomes an advantage, as these radicals inflict immediate oxidative damage on nearby EPS components, cleaving polysaccharide chains, oxidizing proteins, and degrading eDNA. This localized “chemical cutting” progressively dismantles the biofilm’s structural integrity and permeability barrier. Furthermore, the nanoscale dimensions and tunable surface chemistry of POM assemblies facilitate deep diffusion into the biofilm. Critically, the acidic and often H_2O_2 -enriched microenvironment typical of chronic biofilm-associated infections (e.g., in non-healing wounds) amplifies this process by maximizing POM catalytic activity and supplying substrate (H_2O_2) for ROS generation, creating a self-amplifying cycle of biofilm disintegration [96, 97].

Building on this mechanism, recent studies provide compelling evidence for the biofilm-disrupting capabilities of POM nanozymes. For instance, Soria-Carrera et al. developed a covalent polyoxometalate-polypeptide hybrid nanoassembly (POMlymer POMK₁₀) that functions as a POD surrogate with potent antibiofilm properties. The system was synthesized via ring-opening polymerization of amino acid N-carboxyanhydrides on a bis-amino functionalized Mn-Anderson-type POM scaffold, followed by self-assembly into spherical nanoparticles approximately 70 nm in diameter. In catalytic assays, these covalent nanoassemblies exhibited enhanced POD-like activity relative to the parent POM, effectively oxidizing both cationic TMB and anionic ABTS substrates. This enhancement was attributed to the formation of a favorable catalytic pocket within the nanoparticle core, a feature absent in ionic POM-peptide mixtures (K₁₀/POM), which showed negligible activity. In biological assays, POMK₁₀ demonstrated effective antibacterial action against *Staphylococcus epidermidis* (MIC = 125 $\mu\text{g/mL}$) and, importantly, significantly inhibited biofilm

formation. Mechanistic studies revealed distinct behaviors between different POM systems. The parent POM and ionic hybrid induced non-lethal ROS production, which paradoxically promoted biofilm formation as a bacterial stress response. In contrast, the covalent POMlymer exerted its primary antimicrobial effect through membrane disruption, similar to cationic antimicrobial peptides, without promoting adaptive biofilm growth. This work underscores that covalent conjugation in POM-peptide hybrids is crucial for forming stable, self-assembled nanostructures that synergistically combine redox catalysis with targeted antimicrobial and antibiofilm activity, offering a promising strategy for designing advanced antibacterial materials [98]. Along this line, Zhu et al. reported a ROS reservoir based on a polyoxometalate (POM) and metal-organic framework (MOF) hybrid (CuPOM-MOF@S) for efficient antibiofilm therapy and wound healing (Fig. 14). The material was constructed by encapsulating Keggin-type POMs with Cu^{2+} counterions within the pores of HKUST-1, followed by CTAB coating to enhance bacterial capture. It exhibited excellent POD-like activity, enabling cascaded generation of hydroxyl radicals ($\cdot\text{OH}$) at ultra-low concentrations ($5\text{ }\mu\text{g}\cdot\text{mL}^{-1}$) with trace H_2O_2 (0.1 mM). This ROS reservoir achieved over 99% eradication of both *S. aureus* and *E. coli*, while significantly inhibiting biofilm formation. Mechanistic studies revealed that the generated $\cdot\text{OH}$ exerted synergistic antibacterial effects via multiple pathways, including disruption of membrane integrity, induction of oxidative stress, DNA damage, and suppression of biofilm matrix synthesis. In a mouse model of skin infection, the material effectively cleared bacteria and accelerated wound closure, with good biocompatibility. Overall, this work highlights a promising non-antibiotic strategy for combating biofilm-associated infections [99].

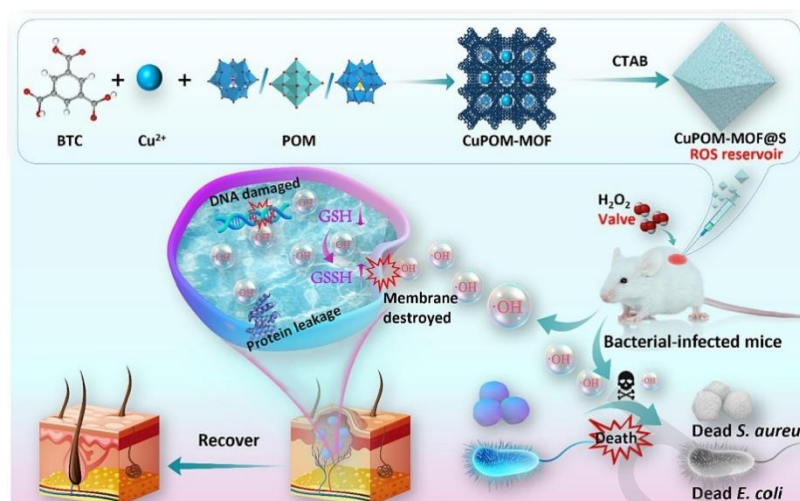


Figure 14 Schematic illustration of the preparation of CuPOM-MOF@S, and its antibacterial activity and application in treating bacterial infections. (BTC = benzene tricarboxylate). Reproduced with permission from Ref. [99], © Elsevier 2023.

In addition to strategies involving covalent peptide conjugation or MOF integration, Chakraborty et al. developed a hybrid hydrogel through the supramolecular self-assembly of Keggin-type POMs (phosphotungstic acid, PTA, or silicotungstic acid, STA) with guanosine monophosphate (GMP), as shown in Fig. 15. This hydrogel exhibits halo peroxidase-like activity for antibacterial and antibiofilm applications. The material was readily prepared by simple mixing, forming a three-dimensional network of highly entangled nanofibers with good mechanical strength, thixotropy, and thermoreversibility. Catalytically, the hydrogel, particularly the PTA-GMP system, efficiently oxidized iodide ions (I⁻) to hypoiodous acid (HOI) in the presence of H₂O₂, demonstrating strong haloperoxidase-mimicking activity with high selectivity for I⁻ over Br⁻ across a broad pH range. Biologically, the PTA-GMP hydrogel, in combination with NaI and low-concentration H₂O₂, exhibited potent bactericidal effects against both Gram-negative *E. coli* and Gram-positive *B. subtilis*, achieving more than 99.9% inhibition. Importantly, the system effectively inhibited biofilm formation. Crystal violet quantification showed biofilm inhibition rates of 92.8% for *E. coli* and 88.1% for *B. subtilis*, outperforming the PTA solution alone. Mechanistic studies revealed that the catalytically generated HOI disrupts bacterial quorum sensing by halogenating

signaling molecules, thereby impeding biofilm development. Moreover, the hydrogel demonstrated enhanced biocompatibility compared to bare POMs and exhibited film-forming capability, highlighting its potential as a coating for antifouling surfaces. Collectively, this work provides a simple and effective strategy for designing smart, biocompatible antibiofilm hydrogel materials based on enzyme-mimetic activity [100].

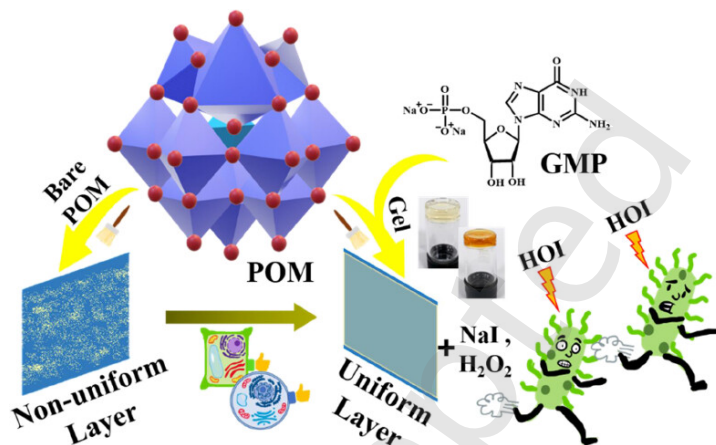


Figure 15 Schematic illustration of the self-assembly between Keggin-type POMs (phosphotungstic acid, PTA, or silicotungstic acid, STA) and GMP. Reproduced with permission from Ref. [100], © American Chemical Society2023.

Expanding on the design of POM-based hydrogels, Mbage et al. developed an organic-inorganic hybrid nanoparticle ($\text{PMo}_5\text{V}_3/\text{CS}$) by immobilizing a vanadium-substituted polyoxometalate ($\text{H}_8\text{PMo}_5\text{V}_3\text{O}_{40}$) onto chitosan (CS). The composite retained the Keggin structure of the POM and formed nanoparticles with a rough surface morphology and an average size influenced by pH and CS/POM ratio. In terms of catalytic function, $\text{PMo}_5\text{V}_3/\text{CS}$ exhibited dual enzyme-mimetic activities, functioning as both a POD and an oxidase. It efficiently decomposed H_2O_2 to generate $\cdot\text{OH}$ and ROS, displaying a notably low apparent Michaelis constant ($K_m = 0.027 \text{ mM}$), indicative of high affinity for H_2O_2 . The material maintained stable catalytic activity across a broad pH range (3-8). Regarding biological activity, $\text{PMo}_5\text{V}_3/\text{CS}$ showed significant antibacterial effects against *E. coli*, with the highest dose (0.9 mg/mL) combined with H_2O_2 achieving strong bacterial growth inhibition. Importantly, the hybrid also effectively disrupted pre-existing biofilms and prevented

new biofilm formation, outperforming H_2O_2 alone. The antibiofilm activity arises from the synergistic combination of CS-mediated membrane destabilization and POM-induced oxidative damage to bacterial membranes and the electron transport chain, resulting in morphological deformation and decreased bacterial viability. This study introduces a stable, reusable, and biocompatible POM-biopolymer hybrid that integrates enzymatic and membrane-disruptive functionalities, offering a promising strategy for the development of antibacterial and antibiofilm agents against bacterial infections [101].

Other antibacterial strategies. Beyond photocatalytic antibacterial approaches and biofilm disruption, POM-based nanozymes have emerged as a versatile antimicrobial platform. Their modes of action can be further diversified, encompassing strategies such as synergistic use with antibiotics, mechanical bactericidal activity, and microenvironment modulation. A notable strategy involves leveraging the ROS-generating capability of nanozymes to compromise bacterial structures, thereby reducing resistance and potentiating the efficacy of conventional antibiotics. For example, one study described a highly efficient and selective antimicrobial composite nanomaterial—isonicotinylhydrazide (INH)-coated POM-functionalized silver nanoparticles (AgNPs). INH served as both a reducing and capping agent during AgNP synthesis, followed by surface modification with phosphotungstic acid (PTA) or phosphomolybdic acid (PMA) to yield a nanosystem with multiple antimicrobial mechanisms. The composite displays robust POD-like activity, catalyzing ROS generation to disrupt bacterial membrane structures and induce oxidative stress. Additionally, it synergizes with the first-line anti-tuberculosis drug INH, markedly enhancing antibacterial efficacy against *S. aureus* and *E. coli*. Importantly, these nanoparticles exhibit low cytotoxicity in mammalian cells and favorable biocompatibility, offering a valuable model for the development of novel, safe, and highly effective antimicrobial nanomedicines [102].

Recent antibacterial strategies have focused on designing smart nanomaterials capable of sensing and adapting to the bacterial microenvironment (BME) to achieve precise and effective antimicrobial effects (Fig. 16). This work describes a POD-

mimetic polyoxometalate-based tri-assembly (**EuW₁₀/Spm/GL-22**) that adaptively responds to the BME, thereby markedly enhancing antibacterial efficacy. The authors created a multifunctional nanocomposite with both fluorescence enhancement and potent antibacterial activity by co-assembling a europium-containing POM (**EuW₁₀**) with the biogenic amine spermine (Spm) and the cationic peptide GL-22 derived from the HPV E6 protein. This tri-assembly exhibits excellent POD-mimetic activity, enabling it to catalyze endogenous H₂O₂ within bacteria to generate abundant ROS. Its positively charged surface further enhances interaction with bacterial membranes and promotes cellular uptake. Consequently, it effectively kills *S. aureus* and *E. coli*. Notably, the material displayed adaptive responsiveness to BME during the bactericidal process, allowing “on-demand” ROS release in the infected microenvironments while minimizing toxicity to normal mammalian cells, thereby demonstrating excellent biocompatibility and translational potential. Overall, this study provides useful guidance for developing novel, environment-responsive, highly potent, and low-toxicity antibacterial nanomaterials [103].

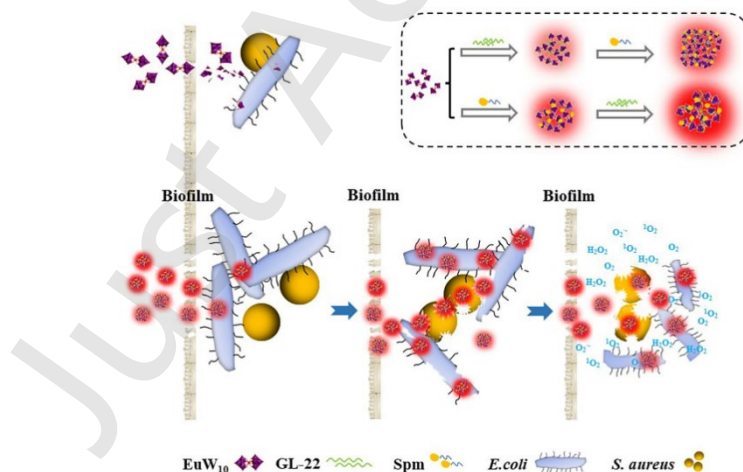


Figure 16 Stepwise fluorescence enhancement of the assemblies and the corresponding improvement in their antibacterial activity. Reproduced with permission from Ref. [103], © MDPI2023.

As an antibacterial strategy based on physical disruption, mechano-bactericidal approaches have garnered increasing interest in recent years. These methods rely on designing material surfaces with defined topological features that mechanically

compromise bacterial cell membranes. For instance, a composite nanomaterial—phosphomolybdate-doped zeolitic imidazolate framework-8 (PMA@ZIF-8) was reported to exhibit pronounced antibacterial activity. This material maintains a high specific surface area and intrinsic porosity, while presenting a rough topological surface decorated with nanorod-like protrusions. Compared with its individual components, PMA@ZIF-8 demonstrated significantly enhanced antibacterial efficacy against *E. coli*, with a reduced minimum inhibitory concentration of $375 \mu\text{g mL}^{-1}$, a 4.35-fold increase in bactericidal kinetics, and a 3-log reduction in bacterial viability within 7 h. Mechanistically, the antibacterial performance of PMA@ZIF-8 arises from the synergistic combination of oxidative nanozyme activity and morphology-driven mechanical membrane disruption. This finding highlights a novel approach for designing dual-functional antibacterial surfaces that integrate both chemical oxidation and physical bactericidal effects [104].

Moreover, the growing crisis of antimicrobial resistance, particularly in Gram-negative pathogens, underscores the need for alternative therapeutic agents that operate through mechanisms distinct from those of traditional antibiotics. In this context, nanozymes, which are nanomaterials with enzyme-like properties, represent a promising platform for targeted antimicrobial therapy. In this work, copper- and iron-containing phosphotungstate nanozymes (Cu, Fe-PTs) were successfully synthesized with dual enzyme-like activities, namely POD-like and GSH oxidase-like activities, as shown in Fig. 17. In the presence of low concentrations of H_2O_2 , these nanozymes efficiently generate ROS such as $\cdot\text{OH}$ and $\cdot\text{O}_2^-$, while simultaneously depleting intracellular reduced GSH, thereby inducing a dual oxidative stress mechanism that selectively suppresses Gram-negative bacteria. Antibacterial experiments demonstrated inhibition rates of approximately 99.4% against *E. coli* and 99.9% against ampicillin-resistant *E. coli* (AREC). Moreover, bacterial binding enhanced the nanozymes' affinity for H_2O_2 and improved system stability. Cytotoxicity assays further confirmed favorable biocompatibility. Overall, this work presents an effective and safe nanozyme-based strategy for targeted antibacterial therapy [105].

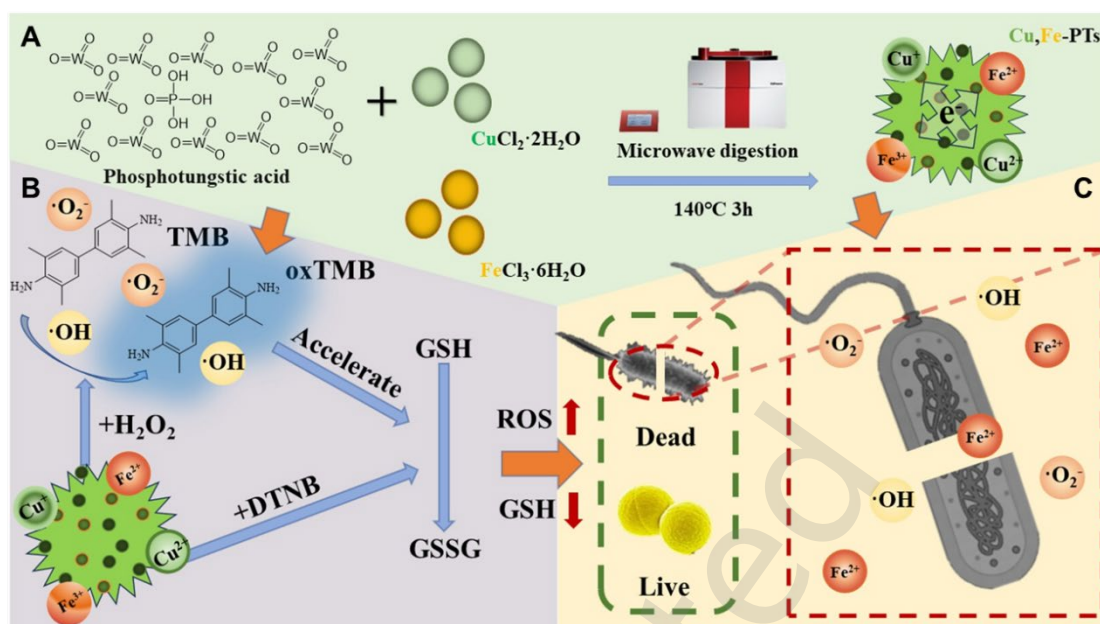


Figure 17 Schematic diagram of the Cu, Fe-PTs synthesis process and antibacterial mechanisms. (A) Cu, Fe-PTs synthesis process. (B) Proposed mechanism underlying the POD-like activity and GSH oxidase-like activity of Cu, Fe-PTs. (C) Schematic illustration of the targeted antibacterial action of Cu, Fe-PTs-based nanozymes against Gram-negative bacteria. Reproduced with permission from Ref. [105], © American Chemical Society2024.

In the development of polyoxometalate-based nanozymes, mimicking OXD activity to generate ROS has emerged as an effective antibacterial strategy. Recently, a **PW₁₂@ZIF-67-Au** nanoreactor was engineered based on this concept. Owing to its intrinsic OXD-like activity, the nanoreactor catalyzes the conversion of oxygen into ·O₂⁻ without requiring exogenous H₂O₂, enabling efficient antibacterial action against both Gram-positive and Gram-negative bacteria (Fig. 18). Experimental results demonstrated that **PW₁₂@ZIF-67-Au** exhibits antibacterial efficiencies exceeding 90% against *S. aureus* and *E. coli* at a concentration of 200 µg/mL. Mechanistically, its bactericidal activity is primarily attributed to ROS-induced membrane damage and oxidative stress. This design not only broadens the application scope of POM-based nanozymes in ROS-driven antibacterial pathways but also highlights the potential of nanoreactor structures to optimize enzymatic activity and selectivity, offering experimental support for the development of next-generation intelligent antibacterial

materials [106].

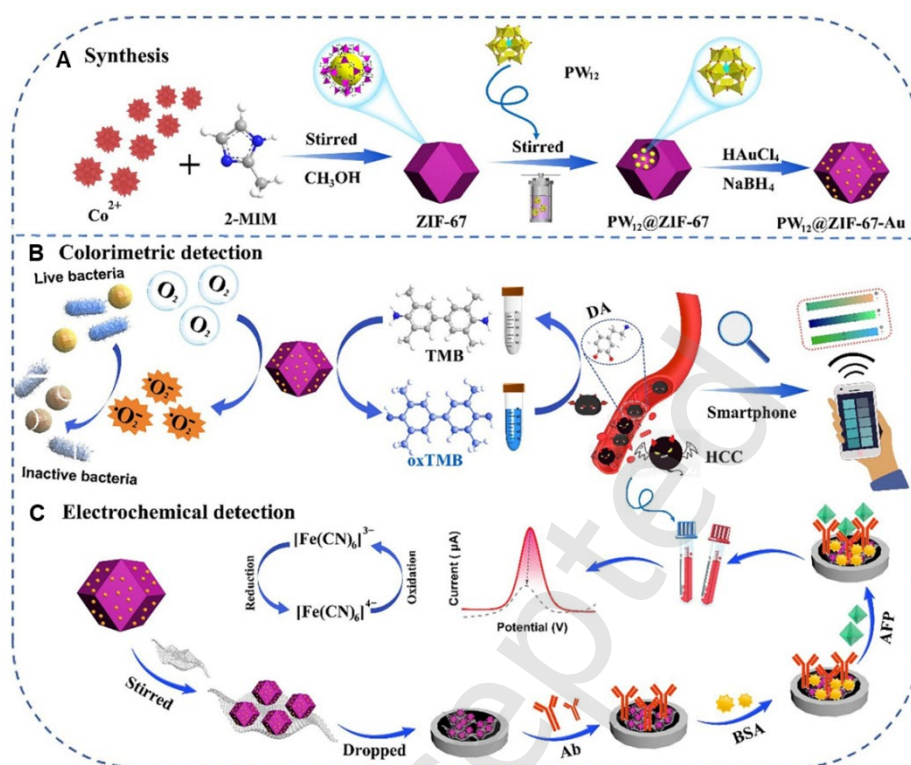


Figure 18 Schematic illustration of the synthesis of PZA and its dual-mode sensing and antibacterial activity: (A) synthesis of PZA. (B) smartphone-assisted colorimetric mode visual detection of DA and antibacterial activity based on the oxidase-mimicking activity of PZA. (C) construction and sensing mechanism of the PZAG-ECI-sensor for AFP. Reproduced with permission from Ref. [107], © Tsinghua University Press 2025.

Table 4 summarizes the representative POM-based nanozyme systems for antibacterial and biofilm eradication, detailing POM composition, enzyme function, catalytic trigger, ROS direction, target bacteria, synergistic approach, and biosafety. In summary, POM nanozymes kill bacteria primarily through ROS ($\cdot\text{OH}$, O_2^-) generated by POD/OXD activities, causing oxidative damage to membranes, DNA, and biofilms. Enhancement strategies include photothermal amplification, responsive activation, and synergistic combinations with polymers or antibiotics. A key trend is the shift from planktonic killing to biofilm eradication. However, challenges remain: high required concentrations, off-target toxicity, and lack of clinically relevant in vivo models. Future directions include ultra-low-dose self-amplifying systems and non-ROS mechanisms

such as disrupting quorum sensing or metabolic pathways.

Table 4. Summary of POM-based nanozyme systems for antibacterial and biofilm eradication^a

En- try	POM central/catal- ytic center	Composite platform/auxilia- ry components	Enzyme - mimetic function	Domina- nt catalytic process	Target bacter- ia	Synergist ic approach /source	Biosaf- ety
1	{GdP ₅ W ₃₀ } [89]	GdP ₅ W ₃₀ @WS ₂ (POM + WS ₂ nanosheets with PEG)	POD	W ⁶⁺ /W ⁵ + cycling → H ₂ O ₂ → ·OH	<i>S. aureus</i> , <i>E. coli</i>	CDT (POM) + PTT (GdP ₅ W ₃₀ @WS ₂)	Low toxicity
2	{GdW ₁₀ O ₃₆ } [90]	—	POD	Acid- triggere d aggrega- tion + W ⁶⁺ /W ⁵ + reductio n → ·OH	<i>E. coli</i> , <i>S. aureus</i>	PTT (POM) + CDT (POM)	Superior biocompat- ibility
3	Fe-POM [91]	Fe-POM@HA hydrogel	POD, CAT, GPx	Fe ²⁺ /M ⁵ + cycling → H ₂ O ₂ → ·OH	<i>MRSA</i>	PTT (POM)	No significant toxicity
4	{MnMo ₆ O ₁₈ } [98]	POMlymers (POM + polypeptide K10)	POD	Catalyti- c pocket → membra- ne disrupti- on + ROS	<i>S. epider- midis</i>	—	—
5	{SiW ₁₂ O ₄₀ } /{PW ₁₂ O ₄₀ }	CuPOMMOF@ S (BTC + POM)	POD	Cascade d ·OH	<i>S. aureus</i>	—	High biocompat

	$\{\text{PMo}_{12}\text{O}_{40}\}$ [99]	$+\text{Cu}^{2+} +$ CTAB)		generati on (ultral w H_2O_2)	<i>s, E. coli</i>		ibility
6	$\{\text{PW}_{12}\text{O}_{40}\}/\{\text{SiW}_{12}\text{O}_{40}\}$ [100]	PTA-GMP/STA -GMP hydrogel	Haloper oxidase	$\text{I}^- \rightarrow$ HOI, HOI $\rightarrow$ $\text{O}_2 + \text{I}^-$	<i>E. coli,</i> <i>B. subtilis</i>	—	Cell survival rate: 75.2%
7	$\{\text{PMoV}_3\text{O}_{40}\}$ [101]	PMoV_3/CS	POD, OXD	H_2O_2 $\rightarrow \cdot\text{OH}$	<i>E. coli</i>	—	—
8	$\{\text{PW}_{12}\text{O}_{40}\}/\{\text{PMo}_{12}\text{O}_{40}\}$ [102]	$\text{AgNPs}^{\text{INH@PTA}}/$ $\text{AgNPs}^{\text{INH@PMA}}$	POD	ROS burst	<i>S. aureu</i> <i>s, E. coli</i>	Combine d with antibiotic (INH)	Low cytotoxicit y
9	$\{\text{EuW}_{10}\}$ [103]	$\text{EuW}_{10}/\text{Spm/GL}$ -22 tri-assembly	POD	ROS generati on	<i>S. aureu</i> <i>s, E. coli</i>	—	—
10	$\{\text{PMo}_{12}\text{O}_{40}\}$ [104]	PMA@ZIF-8	POD, OXD	ROS generati on	<i>E. coli</i>	—	—
11	Cu,Fe-POM [105]	—	POD	Fe^{2+}/F $\text{e}^{3+},$ Cu^{2+}/C u^+ cyclin g $\rightarrow \cdot\text{OH}$ $+ \cdot\text{O}_2^-$ genera tion + GSH consu mption	<i>E. coli,</i> <i>AREC</i>	—	Good biocompat ibility
12	$\{\text{PW}_{12}\text{O}_{40}\}$	$\text{PW}_{12}\text{@ZIF-67-}$	OXD	O_2	<i>S.</i>	—	—

^aHA = hyaluronic acid. MRSA = methicillin-resistant *Staphylococcus aureus*. POMlymers = covalently conjugated POM-peptide hybrid materials. *S. epidermidis* = *Staphylococcus epidermidis*. BTC = benzene tricarboxylate. CTAB = hexadecyltrimethylammonium bromide. GMP = guanosine monophosphate. PTA = phosphotungstic acid, {PW₁₂O₄₀}. STA = tungstosilicic acid, {PW₁₂O₄₀}. HOI = oxidized halogenated species. CS = chitosan. PMA = phosphomolybdic acid, {PMo₁₂O₄₀}. INH = isonicotinylhydrazide. AgNPs = silver nanoparticles. Spm = biogenic amine of spermine, GL-22 = arginine-rich peptides. AREC = ampicillin-resistant *Escherichia coli*. “—” indicates that it is not reported in the cited references.

6. Summary and Future Perspectives

6.1 Current major challenges

Despite their considerable promise in antibacterial therapy, the clinical translation of POM-based nanozymes faces several interconnected and major challenges. The first is long-term biosafety and potential toxicity. The metabolic fate, biodistribution, and possible accumulation of metal ions released from POM structures within the body remain insufficiently understood and require rigorous evaluation. In particular, comprehensive *in vivo* studies are essential to fully elucidate clearance pathways, chronic toxicity profiles, and the risks of organ-specific damage or unintended immune activation. Addressing these issues is essential for any therapeutic application.

A second principal challenge is the unresolved structure-function relationship at atomic resolution. While it is recognized that Keggin, Dawson, Anderson, and wheel-shaped POM clusters show different enzyme-mimicking functions, quantitative relationships between selective structural features (e.g., type and number of heteroatoms, lacunary sites, transition-metal substitution, assembly state) and catalytic parameters remain insufficiently established. For example, why vanadium substitution selectively improves POD-like function whereas tungsten-based POM clusters favor SOD/CAT remains largely empirical. The influence of cluster size, shape, surface charge density, and counterions on catalytic performance also remains underexplored. This lack of mechanistic understanding hampers the rational engineering of POM

nanozyme systems with desired functions.

Furthermore, achieving an optimal balance between high catalytic activity and precise selectivity remains a significant design hurdle. Although robust ROS generation is central to the antimicrobial efficacy of these nanozymes, it is inherently non-discriminatory and may cause “off-target” damage to healthy host tissues if not carefully regulated. Further development therefore requires innovative strategies to confine or trigger their catalytic activity at infection sites, such as microenvironment-responsive activation triggered by bacterial enzymes or localized pH variations. Such approaches will be essential for maximizing therapeutic efficacy while minimizing collateral tissue damage.

The treatment efficacy of nanozyme system-based treatments is strongly dependent on local accumulation at the target lesion. However, the delivery efficiency of POM clusters to pathological tissues, particularly across physiological barriers such as the blood-brain barrier (for neurodegenerative disorders) or the mucus layer (for colitis), remains limited. Surface engineering with targeting ligands, cell-membrane coating, or incorporation into hydrogels can enhance tissue homing, but systematic studies comparing different delivery approaches remain limited.

Another major challenge is the discrepancy between catalytic mechanisms characterized in buffer solutions and the actual biological activity within cells or tissues. Most current studies report ROS scavenging or generation activities using abiotic assays (e.g., ABTS, DCFH, ESR with fixed H_2O_2 concentrations), which fail to capture the complex intracellular environment. Furthermore, POMs may unintentionally perturb endogenous redox signaling networks, such as NF- κ B, Nrf2, and MAPK pathways, raising concerns about off-target effects. Therefore, future evaluations should integrate transcriptomic, proteomic, or phosphoproteomic analyses to comprehensively assess how POM nanozymes rewire cellular signaling. Such evidence is necessary to determine whether POMs act as nonselective redox modulators or can be engineered for selective signaling modulation. Specifically, intracellular pH and electrolyte variations dynamically modulate the catalytic sites of POMs, thereby governing their enzyme-mimicking activities and metabolic fate, which remains a

critical yet underexplored hurdle for clinical translation.

6.2 Future Perspectives

Looking ahead, the development of POM-based nanozymes is expected to progress along several sophisticated and interconnected directions. First, biosafety and clearance behavior should be addressed through rational engineering of biodegradable POM clusters. Engineering POM clusters with controlled degradability, for example by incorporating hydrolysis-sensitive linkers, designing ultrasmall clusters (<5 nm) for renal filtration, or constructing POM-based prodrugs that degrade after performing their catalytic function, represents a promising strategy. Long-term *in vivo* toxicity evaluations in large animal models and systematic assessment of immune responses are essential before clinical translation can be considered.

At the same time, greater attention should be directed toward developing biodegradable POMs. To address long-term biosafety concerns, novel POM structures must be designed to perform their therapeutic functions and subsequently undergo controlled degradation into non-toxic byproducts within the body. Prioritizing metabolic clearance and material life cycle is essential to ensure both clinical translatability and environmental safety of these nanomaterials.

Second, resolving structure-function relationships through high-throughput screening and computational modeling should be given priority. Integrating *in situ* characterization (e.g., X-ray absorption spectroscopy, cryo-EM) with density functional theory (DFT) calculations and machine learning may accelerate the discovery of POM motifs with improved catalytic selectivity and efficiency. Such efforts would support a transition from empirical observation to prediction-guided design.

Furthermore, the integration of multimodal synergistic therapy represents an important frontier. Beyond stand-alone catalytic activity, the next generation of POM nanozymes will likely be engineered as platforms that combine catalytic therapy with other therapeutic modalities, such as immunotherapy, gene therapy, or photothermal treatment. This combinatorial strategy may address complex biological challenges,

such as biofilms or persistent infections, through coordinated mechanisms, overcoming the limitations associated with any single treatment approach.

In conclusion, POM-based nanozymes constitute a highly promising class of therapeutic agents, because of their highly tunable structures and versatile enzyme-mimicking activities. Their ability to catalyze ROS generation and modulate cellular redox states offers strong potential for targeted treatments against bacterial infections, cancer and other diseases. Although challenges persist, particularly regarding biosafety, selectivity, delivery efficiency, and clinical translation, interdisciplinary efforts spanning materials science, chemistry, and biomedicine are gradually addressing these limitations. With ongoing advances in intelligent design, multimodal integration, and biodegradable systems, POM-based nanozymes are well positioned to emerge as a new generation of nanotherapeutic platforms, providing innovative strategies for precision medicine and advanced antibacterial therapies.

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Author Contributions

YC contributed to conceptualization, investigation, and original draft writing. ZY contributed to methodology, investigation, and writing. XK contributed to investigation, review, and writing. MZ contributed to conceptualization, reviewing and editing, project administration, and funding acquisition.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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