Review Article

Constructing multifunctional biointerfaces: Polyoxometalate-based hydrogels—design, functionalization, and translational challenges

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Abstract

Polyoxometalate (POM)-based hydrogels are emerging organic-inorganic hybrid materials that combine the biological functions of POMs with the biocompatibility and tunable mechanical properties of polymer networks. This review summarizes recent advances in their composition design, network engineering, and biomedical applications. Particular emphasis is placed on four representative applications, including wound healing, antimicrobial therapy, localized cancer treatment, and bioelectronics, highlighting the catalytic, redox, photothermal, and electrochemical properties of POMs. The major challenges for clinical translation are also discussed, including the hydrolytic stability of POMs under physiological conditions, the biological contributions of degradation products, scalable manufacturing, and regulatory considerations. Future research should shift from empirical exploration toward mechanism-guided material design. With continued advances in interdisciplinary technologies, POM-based hydrogels are expected to evolve into versatile platforms for precision biomedical applications.

Keywords: polyoxometalates; hydrogels; biomedical applications; smart materials; tissue engineering

1. Introduction

The rapid advancement of tissue engineering, regenerative medicine, and precision medicine has driven a paradigm shift in biomaterial design, evolving from passive structural supports toward intelligent systems capable of dynamic environmental responsiveness and active therapeutic intervention [1, 2]. Within this framework, hydrogels have emerged as versatile platforms for constructing biomimetic tissue interfaces and drug delivery systems, owing to a high water content, three-dimensional network architectures resembling the native extracellular matrix, and favorable biocompatibility [3-6]. Nevertheless, conventional hydrogels suffer from inherent functional limitations, as they typically lack intrinsic catalytic activity, electrical conductivity, redox regulation capability, antioxidant capacity, or specific bioactivity [7-9]. As a result, these materials often fail to meet the increasingly sophisticated therapeutic requirements associated with precise modulation of complex pathological microenvironments.

To overcome these limitations, nanoscale or molecular functional units with well-defined physicochemical properties have been incorporated into hydrogel matrices. This strategy expands the functional capabilities of hydrogels and enables the development of organic-inorganic hybrid systems [10-12]. Among various candidates, polyoxometalates (POMs)—a class of discrete metal–oxygen cluster anions composed of early transition metal atoms interconnected by oxygen bridges—have attracted considerable attention in recent years due to their well-defined structures and highly tunable properties [13-17]. POMs exhibit reversible multi-electron redox activity, remarkable catalytic performance, high photothermal conversion efficiency, and enzyme-mimetic behavior [18-20]. Beyond these physicochemical characteristics, accumulating evidence has revealed their emerging biomedical functionalities, including antibacterial, antioxidant, and immunomodulatory effects [21-23]. Collectively, these attributes render POMs highly attractive molecular building blocks for the construction of intelligent and multifunctional hydrogels.

The integration of POMs into hydrogel networks represents a rational design strategy to achieve synergistic coupling between structural adaptability and functional activity at both molecular and nanoscale levels [24-26]. Compared with simple metal salts, conventional polymers, and other material platforms such as metal-organic frameworks (MOFs) and covalent organic frameworks (COFs), POMs

offer a unique combination of catalytic activity, photothermal conversion, and ion-exchange capability within a single atomically defined molecular cluster [27, 28]. In addition, their excellent solution processability allows their direct integration into hydrogel networks through electrostatic, coordination, or covalent interactions. Through judicious molecular design and crosslinking engineering, POMs can be stably incorporated into biocompatible polymer matrices with tunable mechanical properties, yielding hybrid systems that combine the flexibility of soft matter with the high efficiency of inorganic functional components [29, 30]. Such POM-based hydrogels are capable of responding to specific biological cues or external stimuli, enabling on-demand activation and spatiotemporal regulation of therapeutic functions [31]. Consequently, they offer compelling opportunities to address complex biomedical challenges, including the management of infected wounds, localized cancer therapy, and the development of high-performance bioelectronic interfaces [31-33].

The aim of this review is to systematically summarize recent advances in POM-based hydrogels, with a particular focus on their molecular design principles, functional implementation strategies, and application mechanisms across representative biomedical scenarios. Furthermore, current challenges and future research directions are critically discussed to provide comprehensive insights and forward-looking guidance for the development of next-generation intelligent and functionally integrated biomaterials. Compared with previous reviews, the present review offers three main advances. First, it connects POM structural characteristics with the macroscopic properties of hydrogels from a multiscale perspective. Second, it establishes structure–property relationships by comparing different POM archetypes. Third, it critically discusses POM stability, degradation products, and clinical translation. Together, these aspects provide a framework for the rational design of POM-based hydrogels.

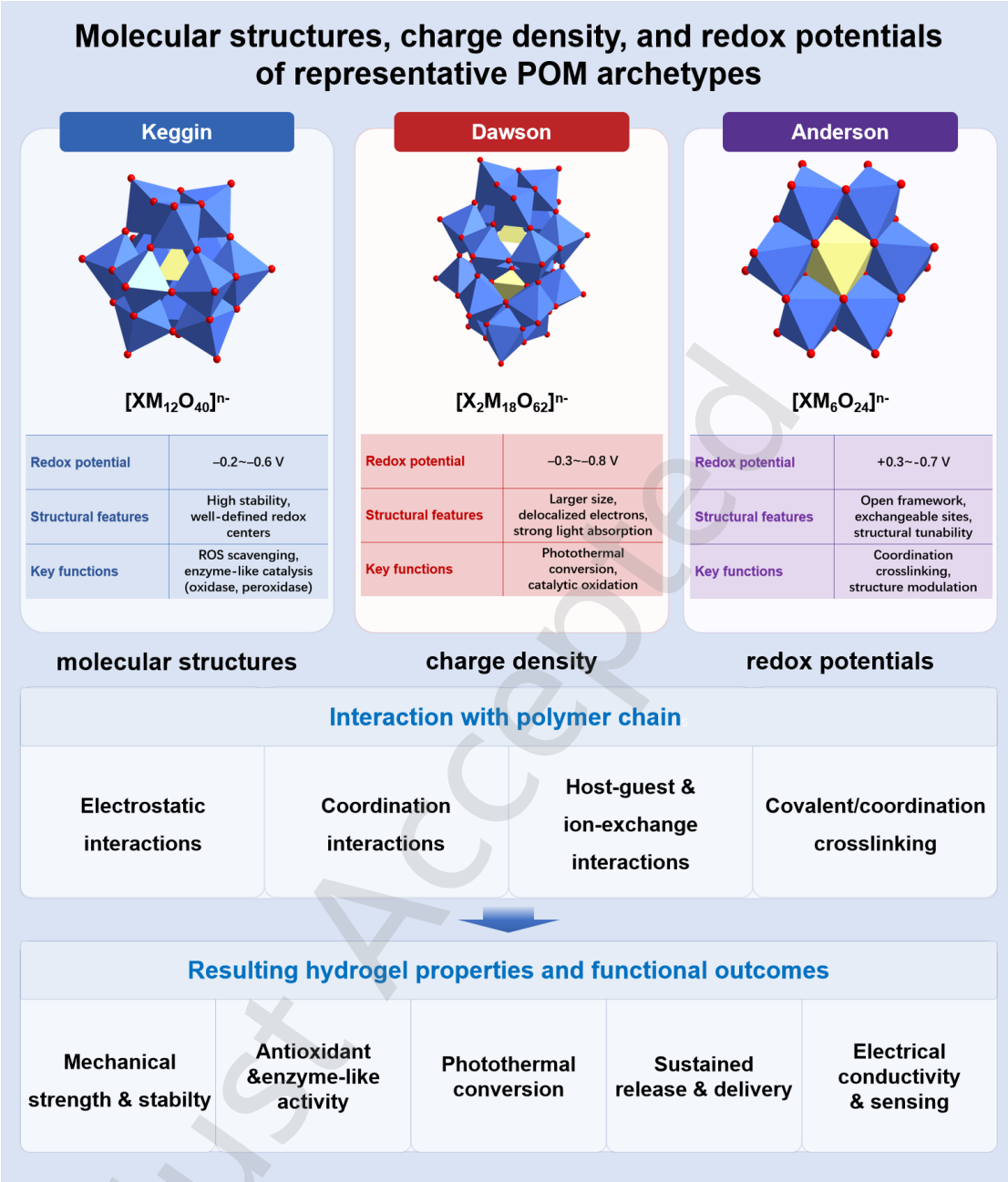

Figure 1 Molecular structures, charge density, and redox potentials of representative POM archetypes

2. Component Design and Synthesis Strategies of POM-Based Hydrogels

The physicochemical properties and biological performance of POM-based hydrogels are governed by the intrinsic functionalities of polyoxometalates, the structural and mechanical characteristics of the polymeric network, and the interfacial synergy established between these components [22, 34]. The design paradigm of such hybrid systems has evolved from simple physical blending toward a systems-

level engineering approach, in which component selection, network architecture, and functional integration are precisely regulated at the molecular and mesoscopic scales.

This section provides an in-depth analysis of the key elements underlying the construction of POM-based hydrogels, including the polymer matrices that furnish a suitable microenvironment for functional POMs, the selection and functionalization of POMs tailored for biomedical applications, and the crosslinking chemistries that enable their stable, controllable, and intelligent integration into unified hybrid networks.

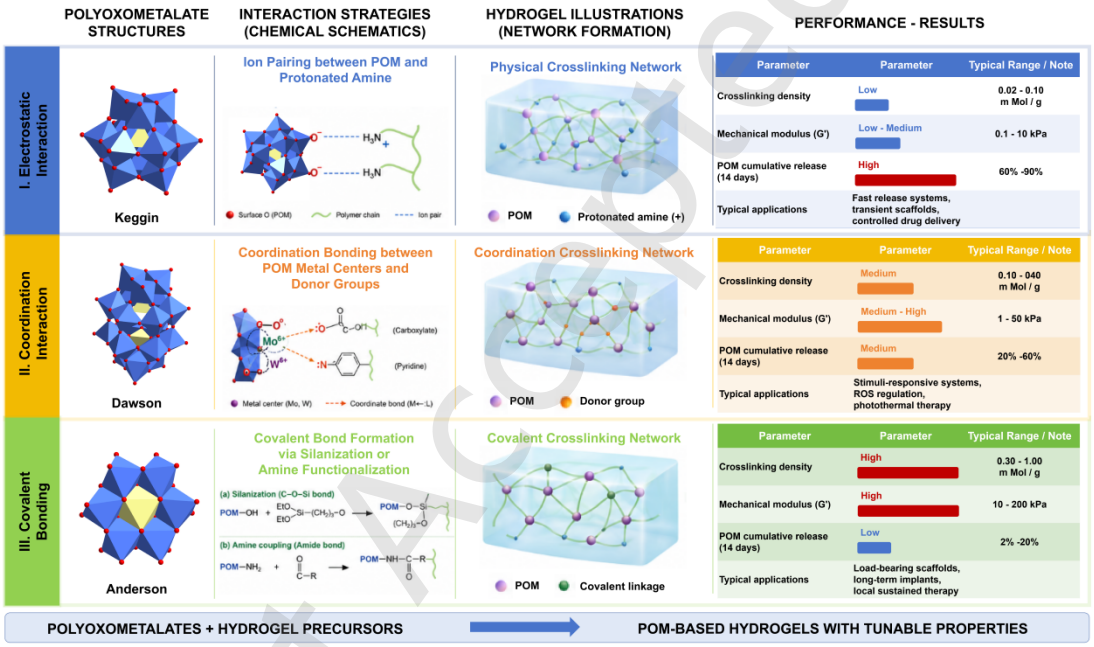

Figure 2 Schematic illustration of three crosslinking strategies for POM-based hydrogels

2.1 Polymer Matrices: Constructing Biocompatible Structural Frameworks

Polymer matrices constitute the three-dimensional network backbone of hydrogels, and their selection directly dictates key material properties, including mechanical performance, swelling behavior, degradation kinetics, and overall biocompatibility [35, 36]. Fundamentally, the formation and stability of a hydrogel are governed by the free energy change of gelation (ΔG_{gel}), which can be expressed as the sum of two competing contributions: the free energy of mixing between polymer chains and water (ΔG_{mix}) and the elastic free energy associated with network deformation ($\Delta G_{elastic}$) [37-39]. The favorable mixing term reflects the intrinsic affinity of hydrophilic polymer segments for water molecules and provides the thermodynamic driving force for solvent uptake and network swelling [40, 41]. In contrast, the elastic

term arises from crosslinking-induced chain confinement and acts as a restoring force that resists unlimited expansion of the polymer network. The dynamic balance between these two factors enables the establishment of a stable, water-rich three-dimensional structure characteristic of hydrogels. Based on their origin and design philosophy, polymer matrices can generally be classified into natural and synthetic categories [42, 43]. When integrated with POMs, these two classes play distinct roles and are associated with different optimization challenges. Natural polymers, such as gelatin, chitosan, hyaluronic acid, and alginate, offer inherent advantages stemming from their intrinsic bioactivity, abundant cell-interactive motifs, and degradability via enzymatic or hydrolytic pathways [44-46]. For instance, the protonated amino groups along chitosan chains can establish strong electrostatic interactions with polyanionic POMs, serving not only as a convenient driving force for gelation but also as preliminary anchoring sites for POM loading [47, 48]. However, hydrogels derived from natural polymers typically suffer from limited mechanical strength and pronounced batch-to-batch variability in their physicochemical properties [49, 50]. Consequently, current research efforts have largely focused on chemical modification strategies or the construction of interpenetrating and hybrid networks to overcome these limitations [51]. Notably, gelatin networks crosslinked via dynamic covalent chemistry, such as aldehyde–amine reactions, combined with physical processing techniques like directional freezing to guide molecular alignment, have enabled the fabrication of composite hydrogels that simultaneously exhibit enhanced mechanical robustness and anisotropic ionic conductivity [52, 53]. Such systems provide promising design paradigms for high-precision biosensors and tissue engineering scaffolds.

In contrast, synthetic polymers—including poly (vinyl alcohol), polyacrylamide, poly (ethylene glycol), and their copolymers—offer nearly unlimited structural tunability and high performance predictability [54, 55]. Parameters such as molecular weight, chain topology, functional group identity, and functional group density can be precisely tailored through polymerization chemistry, allowing rational optimization of interaction modes with specific POMs [24, 56, 57]. For example, incorporation of cationic monomers markedly strengthens electrostatic binding with POMs, whereas the introduction of carboxylate or pyridine moieties enables coordination-driven crosslinking [58]. This level of molecular precision extends to network formation processes: efficient and spatiotemporally controllable crosslinking techniques, including photopolymerization and click chemistry, facilitate the construction of POM-composite hydrogels with uniform architectures and high reproducibility [59]. Accordingly, the selection

of polymer matrices represents an application-oriented optimization process, wherein natural polymers are favored for mimicking extracellular matrix functions and biological signaling, while synthetic polymers are primarily employed to achieve superior mechanical performance, environmental stability, and processing controllability [52]. Regardless of the polymer matrix employed, the primary role of the polymer network is to provide a stable anchoring environment and a suitable reaction microenvironment for POMs [30]. The overall performance of the hydrogel, however, ultimately depends on the intrinsic chemical properties of the POM clusters and the degree of interfacial compatibility between POMs and the polymer network [25, 30].

2.2 Polyoxometalates: Functionally Defined Molecular Components

While the polymer matrix provides the structural framework of the hydrogel, POMs impart their biomedical functions. Within POM-based hydrogel systems, POMs serve as the core of active functions and provide a variety of functionalities. These functionalities originate from the atomically precise metal–oxygen cluster architectures of POMs, which underpin their rich redox chemistry, Lewis acidity, catalytic versatility, distinctive photophysical behavior, and surface characteristics that enable interactions with biomolecules [24, 60, 61]. From a functional perspective, the intrinsic redox activity of POMs underpins their antioxidant and catalytic capabilities by enabling reactive oxygen species (ROS) scavenging and electron-transfer mediation, properties that are particularly critical in antimicrobial and immunomodulatory processes. Meanwhile, the Lewis acidity and distinctive surface charge characteristics of POMs confer a strong propensity for interactions with biomacromolecules and cellular membranes, while also providing a structural basis for their function as nanoscale reactors or catalytic centers. Beyond their biochemical and physicochemical functions, the incorporation of POMs also exerts a pronounced influence on the macroscopic material properties of hydrogels, particularly mechanical performance and swelling behavior [33, 62]. Owing to their high charge density and multivalent coordination capability, POM clusters can act as additional physical or chemical crosslinking nodes within polymer networks, thereby reinforcing network integrity and modulating chain mobility [29, 63]. As a result, POM integration frequently leads to enhanced static mechanical properties, including increased compressive and tensile moduli, elevated fracture stress and strain, and improved overall toughness. In dynamic mechanical analysis, POM-containing hydrogels frequently exhibit higher storage moduli and tunable loss moduli, accompanied by adjustable damping factors, reflecting altered

viscoelastic responses arising from reversible POM-polymer interactions [30]. Concurrently, the strong hydrophilicity and ionic character of POMs significantly affect the hydration behavior of the hydrogel [31, 64]. Their incorporation can increase the overall water content and swelling ratio by introducing additional osmotic pressure and hydration sites. Conversely, when POMs function as multifunctional crosslinkers, they may limit excessive polymer chain expansion, resulting in reduced equilibrium swelling and improved dimensional stability [65, 66]. Moreover, POM-polymer interactions have been shown to regulate swelling and deswelling kinetics, yielding more controlled water uptake and release profiles and enhancing swelling stability over repeated cycles [67]. Such combined regulation of mechanical and hydration properties is particularly critical for maintaining long-term structural reliability and functional consistency in biomedical environments. Consequently, the rational screening or molecular design of POMs for specific biomedical applications is of critical importance and requires a comprehensive understanding of the intrinsic structure–property relationships of different POM architectures, as well as their physicochemical behavior within gel-confined microenvironments [68]. Table 1 summarizes the key structural parameters of different POM structural types and their corresponding influences on hydrogel properties, providing a basis for the rational selection of POMs tailored to specific biomedical applications.

Table 1. Key structural parameters of different POM structural types and their correlations with hydrogel properties.

POM types	Typical Formula	Charge	Size	crosslinking efficiency	redox activity retention	ion conductivity
Keggin [69]	$H_4[SiW_{12}O_{40}]$	4−	~1.0 nm	High; strong electrostatic complexation with chitosan	Moderate	Moderate
Keggin [70]	$H_3[PW_{12}O_{40}]$	3−	~1.0 nm	Moderate; driven primarily by supramolecular assembly	High	Low–moderate
Keggin [71]	Mo-based POM cluster	Polyanionic	~1–2 nm	Moderate–high	Very high; stimulus-triggered valence-state switching	Moderate
Preyssler [72]	$[AgP_5W_{30}O_{110}]^{14-}$	14−	~1.1–1.3 nm	Moderate; hydrogen bonding and network confinement	Moderate–high	High; ion-exchange-mediated transport
Preyssler [73]	$[AgP_5W_{30}O_{110}]^{14-}$	14−	~1.1–1.3 nm	High	Moderate–high	High
Anderson [74]	$[XMo_6O_{24}]^{n-}$ derivative	Moderate-to-high negative charge	~0.8–1.0 nm	Very high; synergistic metal coordination and supramolecular assembly	Moderate–high	Moderate
Dawson [75]	$[P_2W_{18}O_{62}]^{6-}$	6−	~1.1–1.2 nm	High	High	Moderate–high
Isopolymolybdate / POM–	Cu(I)-isopolymolybdate	Polyanionic /	Cluster- to nanoscale	High	High	Moderate

MOF node [76]	cluster or MOF node	framework-associated				
Mo-based POM [77]	Molybdate POM cluster	Polyanionic	~1–2 nm	High; photo-triggered polymerization	High	Moderate
Giant wheel-shaped POM [78]	$\{Mo_{154}\}$	Typically ~14−	~3–4 nm	High	Very high; numerous accessible redox centers	High
Lanthanide-substituted POM [33]	EuW_{10} cluster	Polyanionic	~1 nm	High; combined ionic interactions and physical crosslinking	Moderate	Very high
Electroactive POM [79]	Redox-active Mo/W-based POM	Polyanionic	~1 nm	Moderate	Very high	Very high
Electrochromic POM [34]	Electrochromic POM cluster	Polyanionic	~1 nm	High	Very high	High
POM / cyclodextrin nanonetwork [32]	CDN–POM composite	Polyanionic	Nanocluster / composite scale	Moderate–high	High	Moderate
POM-based antibacterial platform [25]	Redox-active POM cluster	Polyanionic	~1–2 nm	Moderate–high	High	Moderate
Blended POM hydrogel [31]	Blended POM system	Polyanionic	Variable	Moderate	Moderate–high	Moderate

From the perspective of structural suitability, POMs featuring high negative charge density and a good aqueous solubility are more amenable to homogeneous dispersion within polymer matrices and the formation of stable interfacial interactions [13, 68, 80]. Classical Keggin-type POMs, such as phosphotungstic acid, along with Dawson-type analogues, are among the most widely employed species owing to their well-established synthetic protocols, robust structural integrity, and precisely defined charge states [81, 82]. Their strong Brønsted acidity and reversible multi-electron redox properties make them particularly effective for catalytic scavenging of ROS, local pH modulation, and functioning as electron relay mediators [19]. Yang *et al.* [71] reported a molybdenum-based POM-hyaluronic acid hydrogel capable of ultrasound-triggered valence-state switching. In the absence of external stimulation, the hydrogel exploits endogenous hydrogen peroxide to generate ROS via the Russell mechanism, thereby enabling oxygen-independent antibacterial activity under hypoxic conditions. Upon ultrasound activation, accelerated molybdenum redox cycling promotes ROS scavenging, oxygen generation, and macrophage polarization toward a regenerative M2 phenotype, thereby achieving a dynamic transition from antibacterial action to inflammation resolution and tissue repair. This study exemplifies a hydrogen-powered, stimulus-responsive therapeutic paradigm for accelerating diabetic wound healing (Figure 3A).

More distinctive functionalities are observed in Preyssler-type isocaged POMs, whose intrinsic internal cavities can act as nanoscale reactors, enabling selective encapsulation and stimulus-responsive release of therapeutic metal ions (e.g., Ag^{+} and Zn^{2+}) [83]. This unique feature is particularly valuable for antibacterial and pro-regenerative applications. Li *et al.* [72] developed a Preyssler-type POM capable of encapsulating Ag^{+} ions and achieving on-demand release via Na^{+}/Ag^{+} exchange in infection-associated microenvironments. In this system, the POM framework protects Ag^{+} from premature deactivation while ensuring its stable incorporation into the hydrogel network through hydrogen-bonding interactions. Moreover, the integration of extracellular vesicles further promotes angiogenesis, immune modulation, and collagen remodeling. This multifunctional platform demonstrated robust therapeutic efficacy in complex infectious tissue defects, highlighting the role of POMs as precision ion-delivery modules and central nodes for therapeutic co-assembly (Figure 3B).

Despite their promising functionalities, biomedical applications of POMs must carefully balance

chemical activity with long-term biosafety [84-87]. Certain therapeutic effects may be accompanied by partial structural degradation or metal ion leaching, necessitating rigorous evaluation of biological fate and metabolic pathways [88, 89]. In this context, surface functionalization has emerged as a pivotal strategy for optimizing POM performance [57, 90]. Through approaches such as organosilanization and organoamine modification, polymerizable moieties—including vinyl and acryloyl groups—can be introduced onto POM surfaces, enabling their transformation from passive functional fillers into multifunctional crosslinkers or network nodes [24, 91]. Such modifications not only facilitate covalent anchoring of POMs to polymer backbones, thereby minimizing leaching, but also improve dispersion by tuning surface hydrophilicity and hydrophobicity. Additionally, surface engineering may subtly modulate the electronic structure of POMs, allowing fine control over their redox potentials [92, 93]. Collectively, these advances signify an evolution in the role of POMs—from simple functional additives to active, signal-responsive molecular modules capable of executing precisely regulated therapeutic actions in pathological environments.

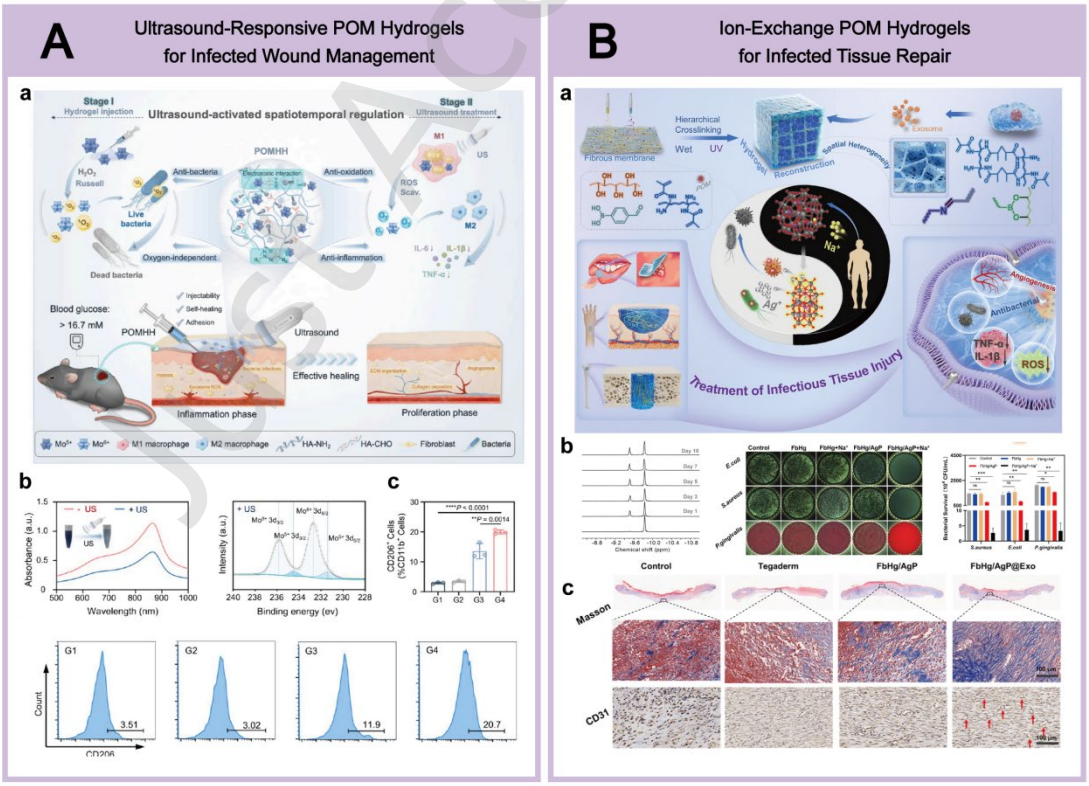

Figure 3 Representative POM-based hydrogel systems for stimulus-responsive antibacterial and regenerative therapy. (A) Molybdenum-based POM-hyaluronic acid hydrogel with ultrasound-

triggered valence-state switching for diabetic wound healing. (a) Schematic illustration. (b) Structural and morphological characterization. (c) In vivo antibacterial, anti-inflammatory, and wound-healing performance. (B) Preyssler-type POM-based multifunctional hydrogel for Ag^{+} encapsulation and infection-responsive release in complex tissue defects. (a) Schematic illustration. (b) Structural and morphological characterization. (c) In vivo antibacterial efficacy and tissue regeneration in infected wound models. (A) is reprinted with permission from Ref. [71], ACS Nano. 2025. (B) is reprinted from the permission from Ref. [72], Advanced Science. 2025.

2.3 Crosslinking Strategies: Constructing Stable and Responsive Network Architectures

The binding modes between POMs and polymer networks fundamentally determine the network topology, mechanical integrity, environmental stability, and reliability of functional expression in POM-based hydrogels [94]. From the perspective of intermolecular interactions, crosslinking strategies can be broadly categorized into noncovalent and covalent approaches [95-97]. In practice, noncovalent or hybrid strategies remain predominant due to their simplicity, processing efficiency, and functional compatibility [62, 98]. These strategies mainly rely on reversible intermolecular forces, among which electrostatic interactions and coordination bonding are the most representative [99, 100]. While such interactions impart dynamic responsiveness and facilitate material processability, their stability is often susceptible to environmental perturbations [101, 102]. In contrast, covalent crosslinking anchors POMs within polymer networks permanently through irreversible chemical bonds, sacrificing part of the dynamic behavior but conferring superior structural robustness, resistance to swelling, and suppression of POM leakage [103, 104]. The three crosslinking strategies exhibit distinct trade-offs in terms of mechanical properties, POM retention, long-term stability, and biocompatibility. Covalent crosslinking generally provides superior structural integrity and the lowest POM leakage, albeit at the expense of more complex synthetic procedures and the potential attenuation of the intrinsic redox activity of POMs [56]. Coordination crosslinking offers stronger and more directional interactions than electrostatic assembly while preserving a certain degree of dynamic responsiveness [62]. In contrast, although electrostatic crosslinking is the simplest to fabricate, it is the most susceptible to variations in ionic strength and exhibits the poorest long-term stability under physiological conditions [105]. The crosslinking strategy determines the network crosslinking density and polymer chain mobility, which together govern the macroscopic stiffness (elastic modulus) of the hydrogel, while POM clusters simultaneously introduce

biochemical cues through their redox activity, surface charge, and metal ion release [106]. At the biointerface, the interplay between matrix stiffness and these biochemical cues profoundly influences cellular behavior [107, 108]. Matrix stiffness primarily activates canonical mechanotransduction pathways, such as YAP/TAZ signaling, through the integrin—focal adhesion—cytoskeleton axis, thereby regulating cell spreading, migration, and stem cell lineage commitment [109]. Meanwhile, the redox activity of POMs modulates local oxidative stress by scavenging or generating ROS, whereas their surface charge and ion release further influence membrane potential and intracellular signaling cascades [110, 111]. Together, these mechanical and biochemical cues establish a coupled physicochemical microenvironment, in which mechanical cues govern how cells perceive and respond to the surrounding matrix, whereas biochemical cues provide functional instructions, such as anti-inflammatory, pro-angiogenic, and antibacterial signals [112]. The coordination between these cues ultimately determines whether the hydrogel promotes tissue integration, fibrotic encapsulation, or functional tissue regeneration in vivo. Therefore, the rational selection of crosslinking strategies must be guided by a comprehensive evaluation of application-specific requirements, including long-term stability, stimulus sensitivity, and self-healing capability.

Among noncovalent strategies, electrostatic interactions represent the most direct and widely employed physical crosslinking mode [113, 114]. This approach exploits Coulombic attraction between polyanionic POMs and positively charged functional groups along polymer chains to drive network formation [47, 115]. The terminal and bridging oxygen atoms on the surface of POM clusters carry a high density of negative charges, enabling the formation of ion pairs with cationic groups on polymer chains, such as protonated amino, quaternary ammonium, and guanidinium groups [116]. A higher negative charge density on POMs and a higher density of cationic groups on the polymer chains lead to stronger electrostatic interactions [117]. In addition, changes in the redox state of POMs (e.g., Mo^{5+}/Mo^{6+} or W^{5+}/W^{6+} conversion) alter their surface charge density, thereby dynamically modulating the strength of electrostatic interactions [63]. At the ionic level, electrostatic crosslinking is also accompanied by the release or exchange of counterions (e.g., Na^+ and H^+), which affects the local ionic balance and osmotic pressure within the hydrogel network [118]. For instance, Huang *et al.* [69] constructed a double-network hydrogel by immersing a preformed chitosan-based primary network into a Keggin-type POM solution, leveraging strong electrostatic interactions between the two components. This strategy significantly

enhanced the mechanical performance of the material, with the fracture strength of the resulting PAM–CH–SiW hydrogel reaching approximately 1.05 MPa (Figure 4 A). However, the strength of ionic crosslinks is highly dependent on the surrounding medium. In physiological environments, abundant salt ions can competitively screen electrostatic interactions, leading to network weakening, POM dissociation, or burst release, thereby limiting the applicability of purely electrostatic systems in long-term implantation scenarios. Accordingly, such hydrogels generally exhibit a relatively high cumulative POM release in physiological media, which may increase the risk of long-term cytotoxicity [119].

Compared with electrostatic crosslinking, coordination-driven crosslinking provides stronger binding and greater directional selectivity [120]. Consequently, this strategy has been extensively investigated. [58, 121]. By designing polymers bearing coordination motifs—such as carboxyl, catechol, or pyridine groups—that can interact with exposed transition metal centers on POM surfaces, more robust and structurally defined networks can be achieved [122]. At the molecular level, the formation of coordination bonds involves σ-donor interactions between the vacant d orbitals of metal centers in POMs and the lone-pair electrons of donor atoms in polymer chains [123]. In some systems, d–π back-donation also contributes to interfacial charge transfer. Coordination interactions can further modify the electronic structure of POMs, thereby regulating their redox potentials [124]. In addition, the responsiveness of coordination bonds to pH or competing ligands originates from the dynamic shift of the coordination equilibrium [125]. Protonation or deprotonation alters the electron-donating ability of the ligands, whereas competing ligands (e.g., phosphate and citrate) can replace the original coordinating groups, leading to the reversible dissociation of crosslinking junctions [126]. Casimiro *et al.* [74] reported a class of Anderson-type POM-based hybrids functionalized with terpyridine groups at both termini, which coordinate with Co^{2+} or Zn^{2+} ions to form linear coordination polymer chains. These chains further self-assemble into fibrous supramolecular networks through interchain electrostatic attraction, ultimately yielding supramolecular gels with strong mechanical properties (storage modulus on the order of 10^4 Pa), along with luminescence, birefringence, and self-healing capabilities (Figure 4 B). Compared to simple electrostatic interactions, coordination bonds typically exhibit higher bond energies and greater spatial directionality, enabling more effective confinement of POMs at network nodes while introducing stimuli-responsive behaviors to changes in pH or competing ligands. In terms of long-term stability, coordination-crosslinked hydrogels generally exhibit intermediate performance between electrostatically

and covalently crosslinked systems [4]. However, their sensitivity to chemical environments, such as high phosphate concentrations or substantial pH variations, should still be taken into consideration. Overall, coordination crosslinking provides a balance between bonding strength and dynamic responsiveness, although its long-term applicability remains dependent on the chemical environment [127].

Recent research has increasingly focused on the development of dynamic and supramolecular crosslinking networks that integrate stability with intelligent responsiveness by combining multiple interaction modes [105, 128, 129]. For example, Guo *et al.* [130] constructed hydrogels based on dual dynamic crosslinking via Schiff base formation and phenylboronate ester interactions, endowing the system with pH- and glucose-responsive drug release capabilities. Additionally, host–guest interactions have been widely employed to introduce self-healing behavior and reversible network reconfiguration. Overall, electrostatic crosslinking is more suitable for short-term and dynamic applications, coordination crosslinking provides a balance between stability and responsiveness, whereas covalent crosslinking is better suited for long-term implantation [127]. However, many POMs, particularly Mo-based Keggin-type clusters, are inherently susceptible to hydrolysis under physiological pH (~7.4), and their stability is strongly influenced by the POM structure, concentration, and buffer system [84]. Lokare *et al.* [131] demonstrated that α-Keggin-type POMs with a high charge density can associate with hydroxypropyl cellulose through a superchaotropic effect, where steric hindrance effectively suppresses hydrolysis and extends their stability from acidic conditions to near-neutral pH. In contrast, highly charged and strongly hydrated POMs that cannot effectively associate with polymer chains, such as $[H_2W_{12}O_{40}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, and $[SiW_{11}O_{39}]^{8-}$, cannot be stabilized to the same extent. These findings demonstrate that the protective effect of hydrogel networks is not universal but depends on the compatibility between the POM structure and the crosslinking strategy [132]. Therefore, when evaluating the biomedical performance of POM-based hydrogels, it is important to distinguish the intrinsic bioactivity of intact POM clusters from the potential contributions of their degradation products, such as metal-oxo fragments or released metal ions, which have themselves been reported to exhibit therapeutic activity in certain systems [133]. These advances reflect the evolution of POM-based hydrogel design from emphasizing static structural stability to developing adaptive systems capable of sensing and responding to complex biological microenvironments. The three major crosslinking strategies exhibit distinct characteristics. Electrostatic

crosslinking relies on ionic pair formation and is characterized by relatively weak bonding, simple fabrication, and excellent dynamic responsiveness [134]. but it is highly sensitive to ionic strength and pH, exhibits limited POM retention, and is therefore best suited for short-term in vitro applications or rapid-response scenarios. Coordination crosslinking is based on directional coordination between ligands and metal centers, providing intermediate bond strength, reversible responsiveness, and moderate POM retention, making it suitable for applications requiring a balance between stability and dynamic behavior [24]. Covalent crosslinking permanently anchors POMs through irreversible covalent bonds, providing the highest bond strength, superior structural integrity, and the best POM retention despite its synthetic complexity and limited dynamic responsiveness, and is therefore preferred for long-term implantation or applications requiring minimal POM leakage [135]. Importantly, crosslinking strategy alone does not determine hydrogel performance. The charge density of POMs, the density of polymer functional groups, and their interfacial compatibility also play critical roles in governing crosslinking efficiency and overall material performance [136]. Therefore, the optimal crosslinking strategy should be selected according to the intended therapeutic duration, the required level of dynamic responsiveness, and the ionic strength and pH of the target physiological environment, rather than relying on a single crosslinking approach [52].

In summary, the fabrication of POM-based hydrogels can be regarded as a process of precise interfacial engineering between polymer networks and POM clusters at both the molecular and supramolecular levels. The key lies in understanding how three interrelated processes at the POM-polymer interface—molecular recognition, ion exchange, and electron transfer—collectively govern the crosslinking strength, response kinetics, and functional performance of the hydrogel [24]. Furthermore, optimizing the material properties requires the coordinated integration of three key elements: a tunable physicochemical environment provided by the polymer matrix, the specific biomedical functionalities endowed by POMs, and stable yet intelligent interconnections established through noncovalent or covalent interactions [56, 137]. Current research has shifted from static assembly toward dynamic integration, with the central challenge lying in balancing functional activity, structural stability, and biological responsiveness. Future breakthroughs are expected to arise from advances in POM surface engineering, the development of novel dynamic crosslinking chemistries, and deeper elucidation of structure–activity relationships within complex biological microenvironments, thereby driving the evolution of POM-based hydrogels into

smarter and safer next-generation biomedical platforms.

The design principles of POM-based hydrogels have been discussed from three complementary perspectives: polymer matrices, POM structural selection, and crosslinking chemistry. These factors do not act independently but collectively determine the overall performance of the hydrogel through interfacial synergistic effects. Specifically, the polymer matrix provides mechanical support and biocompatibility, the POM structure governs the type and magnitude of bioactivity, and the crosslinking strategy regulates their coupling efficiency as well as the accessibility and retention of active POM species under physiological conditions [22]. Understanding this structure-crosslinking-property relationship provides the foundation for the rational design of POM-based hydrogels tailored to specific pathological microenvironments. The following sections illustrate how these design principles translate into therapeutic efficacy and functional performance in representative biomedical applications, including wound healing, antimicrobial therapy, cancer treatment, and biosensing.

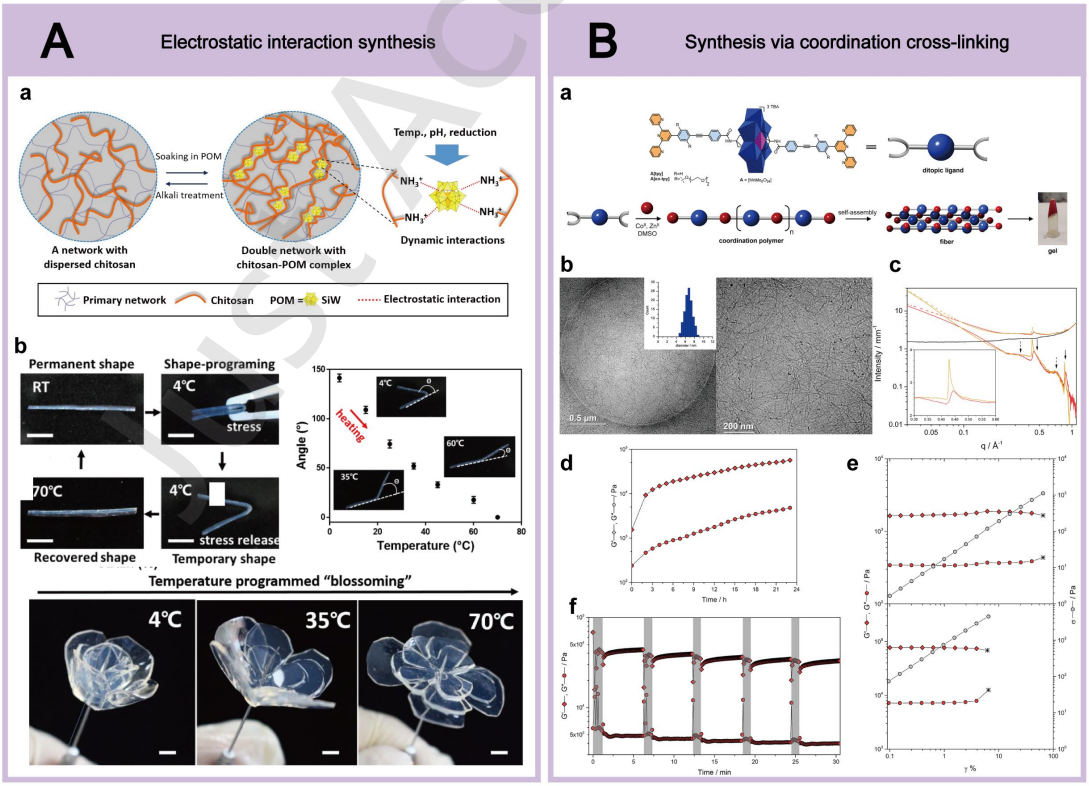

Figure 4 Representative POM-based hydrogels constructed via electrostatic interaction and supramolecular coordination for dynamic and multifunctional materials. (A) Double-network

hydrogel formed by programmable electrostatic interactions between chitosan and POMs, exhibiting enhanced mechanical properties and stimuli-responsive behaviors. (a) Schematic illustration. (b) Structural and morphological characterization. (B) Supramolecular coordination polymer gels based on terpyridine-functionalized Anderson-type POM hybrids and Co^{2+}/Zn^{2+} ions. (a) Schematic illustration. (b) Structural and morphological characterization. (c) Small-angle X-ray scattering analysis. (d) Molecular dynamics simulation of hierarchical fiber assembly. (e) Optical and luminescent properties. (f) Macroscopic gel behavior, birefringence, and self-healing performance. (A) is reprinted with permission from Ref. [69], Chemistry of Materials, 2020. (B) is reprinted with permission from Ref. [74], JACS Au, 2024.

3. Biomedical Applications of POM-Based Hydrogels

The design principles discussed above provide the foundation for understanding the biomedical performance of POM-based hydrogels. The following sections highlight their applications in major biomedical fields and illustrate how rational material design translates into therapeutic efficacy and functional performance.

Owing to their tunable mechanical properties, efficient ion and electron transport capabilities, and the intrinsic catalytic and biological activities of POMs, POM-based hydrogels have demonstrated broad potential across diverse biomedical applications [22, 138-140]. These systems not only exploit POMs as active therapeutic components but also integrate intelligent sensing and programmed intervention. The synergy between POM chemistry and polymeric network architectures enables adaptive functions in complex pathological microenvironments, including chronic wounds, tumors, and infectious lesions [141-145]. From the perspective of POM functionality, these biomedical applications can be broadly classified into three fundamental mechanisms. The redox activity and enzyme-like catalytic behavior of POMs drive ROS regulation and immunomodulation in wound healing and antimicrobial therapy [146]. Their photothermal conversion capability and catalytic activity underpin localized photothermal and catalytic therapies for cancer treatment. Meanwhile, the reversible multielectron-transfer capability and ionic conductivity of POMs enable efficient signal transduction and amplification in bioelectronic sensing [147]. The following sections discuss these applications within the framework of these three mechanistic pathways.

This section systematically discusses the underlying application principles, material design strategies, and recent research progress of POM-based hydrogels in key biomedical domains, including wound healing and tissue regeneration, antibacterial therapy, cancer treatment, and bioelectronics and biosensing. Particular emphasis is placed on elucidating how the unique chemical characteristics of POMs govern material–biological interactions and drive functional outcomes in these systems.

3.1 Wound Healing and Tissue Repair

The redox activity and enzyme-like catalytic behavior of POMs enable the regulation of oxidative stress and the immune microenvironment, which constitutes the fundamental mechanism underlying their wound-healing activity [148]. The refractory nature of chronic wounds, such as diabetic foot ulcers, arises from highly complex pathological microenvironments characterized by persistent inflammation, high susceptibility to infection, excessive oxidative stress, and impaired cellular function [149-151]. Conventional wound dressings primarily provide passive coverage and mechanical protection, making it difficult to simultaneously address microenvironmental regulation and active therapeutic intervention [152, 153]. By integrating POMs endowed with redox regulation, catalytic activity, and ion-exchange capability into biocompatible polymer networks, POM-based hydrogels can be engineered as multifunctional "active dressings" capable of dynamically modulating the wound microenvironment [154, 155].

The core design principle of these systems lies in exploiting the variable valence states and enzyme-mimetic catalytic activities of POMs to execute cascaded therapeutic functions in response to wound-specific biochemical cues, such as elevated hydrogen peroxide (H_2O_2) levels and acidic pH [156]. At the molecular level, POMs mimic the catalytic activities of superoxide dismutase (SOD) and catalase (CAT), converting harmful superoxide radicals ($\bullet O_2^-$) and hydrogen peroxide (H_2O_2) into O_2 and H_2O, thereby directly reducing local oxidative stress [111]. More importantly, the alleviation of oxidative stress further regulates macrophage polarization by suppressing the expression of pro-inflammatory M1 markers (e.g., TNF-α and IL-6) while promoting anti-inflammatory M2-associated factors (e.g., IL-10 and TGF-β), thereby disrupting the persistent inflammatory cycle in chronic wounds [157]. For example, Pu *et al.* [148] developed a smart hydrogel co-loaded with zinc-doped molybdenum-based POM clusters and

glucose oxidase (GOx). In the hyperglycemic milieu of diabetic wounds, GOx catalyzes glucose oxidation to generate H_2O_2, which subsequently triggers the catalase- and superoxide dismutase–like activities of the POMs to scavenge reactive oxygen species and alleviate oxidative stress. Simultaneously, the controlled release of Zn^{2+} ions promotes cellular proliferation and tissue regeneration. Through this cascade of reactions, harmful metabolic intermediates are converted into benign products, while macrophage polarization is driven toward a pro-regenerative phenotype. As a result, this system achieved wound closure rates approaching 90% in vivo, exemplifying a metabolic reprogramming and immune modulation strategy for diabetic wound healing.

Future research directions are expected to focus on the development of next-generation smart wound dressings capable of feedback-responsive behavior toward multiple wound biomarkers, including specific enzymes, pH fluctuations, and ROS levels [158, 159]. Moreover, coupling the catalytic activity of POMs with the spatiotemporally controlled delivery of bioactive agents, including growth factors and extracellular vesicles, provides a promising strategy for individualized and stage-specific wound therapy [160, 161]. However, the clinical translation of POM-based hydrogels for wound healing still faces several critical scientific challenges. Although the enzyme-mimicking activities of POMs have shown promising performance in vitro and in acute infection models, the microenvironment of chronic wounds, such as diabetic wounds, is highly complex [71]. The coexistence of high glucose levels, acidic metabolites, and various proteases may substantially interfere with POM catalytic efficiency, and their long-term activity under realistic pathological conditions remains to be validated [162]. Moreover, current studies have primarily focused on accelerating the healing rate, whereas the quality of regenerated tissue—including scar formation, regeneration of skin appendages (e.g., hair follicles and sweat glands), and the functional integrity of newly formed vascular networks—has received limited systematic evaluation. The long-term accumulation of POM degradation products at wound sites and their potential effects on epidermal stem cell function also remain poorly understood. Addressing these issues will determine whether POM-based hydrogels can progress from experimental studies toward clinical applications.

3.2 Antimicrobial and Anti-Biofilm Therapy

The broad-spectrum antimicrobial activity of POMs arises from their ability to disrupt the bacterial

electron transport chain, disturb intracellular redox homeostasis, and induce membrane interactions through their highly negatively charged surfaces [133]. Bacterial infection, particularly biofilm formation, represents a major obstacle in wound healing and implant-associated infections [163-165]. POMs inherently exhibit antimicrobial activity through multiple mechanisms, including the controlled release of metal ions (e.g., Ag^{+} and Zn^{2+}), the generation of ROS, and enzyme-mimetic haloperoxidase activity that catalyzes the formation of highly oxidative halogenated species [166]. Incorporating POMs into hydrogel matrices enables localized, sustained, and controllable delivery of antimicrobial functionalities, thereby enhancing therapeutic efficacy while minimizing systemic toxicity [25, 31].

A central design strategy involves exploiting the unique structural characteristics of POMs to amplify antibacterial potency while reducing the risk of bacterial resistance [167, 168]. At the molecular level, the antibacterial activity of POMs involves multiple synergistic mechanisms. First, POM clusters with high negative charge densities can adsorb onto bacterial cell walls and membranes through electrostatic interactions, resulting in membrane potential disruption, increased membrane permeability, and leakage of intracellular proteins and nucleic acids [169]. Second, POMs interfere with bacterial electron transport and ATP synthesis by targeting key enzymes involved in the respiratory chain, such as dehydrogenases [133]. Third, POMs can directly oxidize intracellular glutathione (GSH), causing GSH depletion and elevating intracellular ROS levels, thereby inducing oxidative damage [111]. In addition, some POMs can directly interact with bacterial DNA, disrupting DNA replication and repair processes. For instance, Fan *et al.* [73] developed carboxymethyl chitosan–based composite hydrogels by encapsulating Ag^{+} ions within the internal cavity of a Preyssler-type POM (AgP_5W_{30}). Acting as a nanoscale carrier, the POM effectively prevents aggregation and premature inactivation of silver ions, enabling sustained and controllable Ag^{+} release and exhibiting potent antibacterial activity against a broad spectrum of pathogens, including methicillin-resistant Staphylococcus aureus (MRSA). In addition, the resulting hydrogel displays thermoresponsive self-healing behavior, highlighting the feasibility of integrating antimicrobial efficacy with mechanical adaptability (Figure 5A).

An alternative strategy leverages the enzyme-mimetic catalytic activity of POMs to achieve non-antibiotic antibacterial action [170, 171]. Chakraborty *et al.* [70] reported supramolecular hydrogels formed through the self-assembly of phosphotungstic acid (PTA) and guanosine monophosphate (GMP).

In the presence of hydrogen peroxide, PTA acts as a highly efficient haloperoxidase mimetic, catalyzing the conversion of iodide into strongly bactericidal metaiodic acid. This catalytic process not only directly inactivates bacteria but also disrupts bacterial quorum sensing, thereby effectively suppressing biofilm formation. Importantly, this catalytic-based killing mechanism circumvents the reliance on conventional antibiotics, offering a promising route for mitigating the emergence of antimicrobial resistance (Figure 5 B).

Current research trends are increasingly directed toward the development of "on–off" antimicrobial hydrogels that can selectively trigger drug release or activate catalytic functions in infection-associated microenvironments, such as acidic pH or the presence of specific bacterial enzymes [172, 173]. Concurrently, antimicrobial activity is being integrated with anti-inflammatory and pro-regenerative functions to construct dual-functional platforms that simultaneously combat infection and promote tissue repair, thereby addressing the therapeutic demands of complex infectious lesions. It is worth noting that several critical challenges associated with the antibacterial application of POMs require careful consideration. Although the multi-target antibacterial mechanisms of POMs may help delay the emergence of bacterial resistance, their selectivity between bacterial and mammalian cells remains limited, and the potential adverse effects on beneficial microbiota, such as skin commensal bacteria, have not been sufficiently evaluated [169]. More importantly, the dense extracellular polymeric matrix within biofilms presents a substantial diffusion barrier for nanoscale POM clusters [174]. Currently, most studies are based on planktonic bacteria or early-stage biofilm models, whereas systematic data on the eradication efficiency against mature biofilms remain scarce. In addition, whether long-term antibacterial exposure to POMs induces bacterial resistance and whether their multi-target mechanisms can effectively mitigate this risk remain to be verified through systematic long-term serial passage studies.

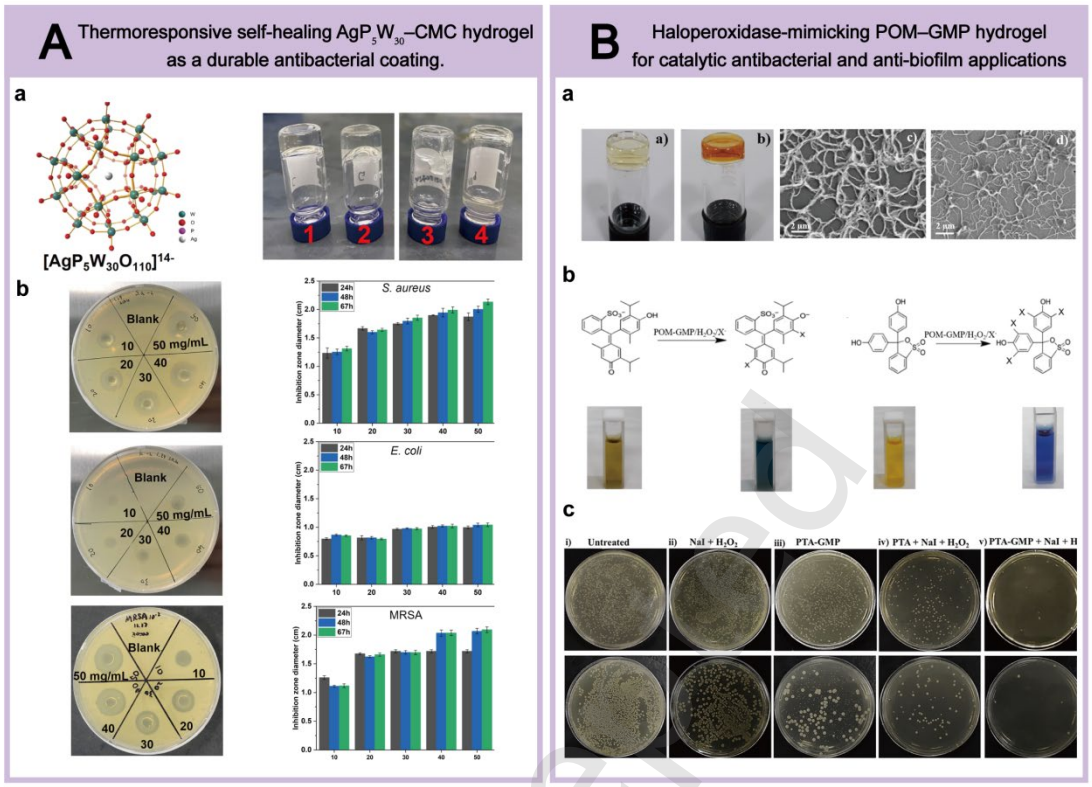

Figure 5 Polyoxometalate-based supramolecular hydrogels with antibacterial coating and biofilm inhibition properties. (A) Thermoresponsive self-healing AgP_5W_{30}-CMC hydrogels. (a) Structural schematic of the $[AgP_5W_{30}O_{110}]^{14-}$ component and photographs of the hydrogel. (b) Agar diffusion assays against S. aureus, E. coli, and MRSA, with corresponding inhibition zone diameters. (B) Haloperoxidase-mimicking POM-GMP hydrogels. (a) Photographs and electron microscopy images of hydrogel morphology. (b) Catalytic oxidation reaction scheme and corresponding solution color changes. (c) Agar plate colony assays of different treatment groups. (A) is reprinted with permission from Ref. [73], Biomacromolecules, 2022. (B) is reprinted with permission from Ref. [70], Biomacromolecules, 2023.

3.3 Cancer Treatment and Collaborative Therapy Platforms

The high photothermal conversion efficiency and catalytic activity of POMs enable the simultaneous induction of localized hyperthermia and ROS-mediated cytotoxicity, providing the dual mechanistic basis for their anticancer activity [175]. A central challenge in localized cancer therapy is achieving high intratumoral drug accumulation and multimodal synergistic treatment while minimizing collateral damage to surrounding healthy tissues [176-178]. POM-based hydrogels offer an attractive platform for local tumor management owing to their injectability, in situ gelation capability, capacity for loading diverse therapeutic agents, and the intrinsic photothermal, catalytic, and chemodynamic therapeutic

potentials of POMs [75].

Within this context, POMs play multifaceted and synergistic roles. At the cellular and molecular levels, the antitumor activity of POMs involves the modulation of multiple signaling pathways [179, 180]. Some POMs elevate mitochondrial ROS levels to activate mitophagy, thereby inducing apoptosis in tumor cells [181]. Sb-rich POMs can simultaneously trigger ferroptosis and apoptosis by increasing lipid peroxidation and regulating the expression of ferroptosis-associated proteins [182]. Anderson-type POMs induce programmed cell death by inhibiting the PI3K/AKT signaling pathway, downregulating the anti-apoptotic protein Bcl-2, and activating Caspase-9 [179]. In addition, POMs can suppress tumor cell proliferation by inhibiting signaling pathways such as STAT3 [183]. Zhang *et al.* [76] designed an injectable chitosan–alginate hydrogel incorporating a Cu(I)-isopolymolybdate-based metal–organic framework. Acting as a sustained reservoir of Cu and Mo ions, the POM nodes continuously catalyze Fenton-like reactions in the mildly acidic tumor microenvironment, generating highly cytotoxic hydroxyl radicals (·OH) for chemodynamic therapy. Simultaneously, the released metal ions participate in metabolic interference, collectively enabling a "three-in-one" therapeutic synergy encompassing chemotherapy, chemodynamic therapy, and metabolic regulation. This work exemplifies the capacity of POM-based hydrogel platforms to orchestrate multiple therapeutic pathways within a confined tumor site.

Beyond catalytic therapy, the photothermal properties of POMs have been effectively integrated into hydrogel-based cancer treatment systems [184, 185]. Li *et al.* [77] developed a near-infrared II (NIR-II)–responsive injectable platform that co-encapsulates molybdate POM clusters and azo initiators. Under 1064 nm laser irradiation, POMs function as photothermal transducers to initiate localized free-radical polymerization, enabling in situ gelation and prolonged drug retention at the tumor site. This light-triggered strategy affords precise spatiotemporal control over treatment localization. Similarly, Guedes *et al.* [78] reported a dual-crosslinked dynamic hydrogel incorporating $\{Mo_{154}\}$ POM clusters, in which chemotherapeutic drugs are released via bond exchange under acidic conditions and near-infrared irradiation, while the POMs simultaneously exert photothermal effects. Such systems highlight the feasibility of combining chemotherapy and photothermal therapy within a single, dynamically responsive hydrogel matrix (Figure 6 A).

Collectively, these studies underscore the potential of POM-based hydrogels as multifunctional local therapeutic reservoirs capable of integrating, sequencing, and amplifying multiple anticancer modalities [22]. Future research directions are expected to focus on the development of more sophisticated response systems activated by tumor-specific enzymes, abnormal redox gradients, or metabolic signatures, as well as the incorporation of diagnostic and imaging functionalities to advance integrated theranostic platforms. However, the clinical translation potential of POM-based hydrogels for cancer therapy largely depends on achieving a balance between tumor selectivity and off-target toxicity, which remains a key unresolved issue. Although local encapsulation within hydrogels and tumor microenvironment-responsive release can substantially reduce systemic exposure to free POMs, the intrinsic cytotoxicity of POMs originates from their heavy metal-based frameworks (e.g., W, Mo, and V), and their high negative charge density may limit their ability to selectively distinguish between normal and cancer cells [186]. Currently, most studies provide only qualitative descriptions of "no systemic toxicity," while quantitative analyses of POM accumulation in major organs remain insufficient. More importantly, different POM structures exhibit considerable variations in their selectivity toward normal and cancer cells, yet systematic structure–activity relationship studies are still lacking to guide rational material selection. The long-term metabolic pathways and chronic toxicity of POM degradation products in vivo, particularly the potential accumulation of W- and Mo-containing species in bone tissues, remain largely unexplored. This issue is especially important for applications involving repeated administration or long-term implantation.

3.4 Bioelectronic and Physiological Sensing

The reversible multielectron-transfer capability and high ionic conductivity of POMs enable efficient signal transduction and amplification, forming the fundamental basis for their application in bioelectronic sensing [147, 187, 188]. Flexible, stretchable, and biocompatible conductive materials are essential for the development of next-generation wearable and implantable bioelectronic devices [189-191]. In this context, POMs—owing to their multicharged, redox-active nanocluster nature—play dual and complementary roles. On the one hand, they function as ionic conductive fillers or physical crosslinking nodes, enhancing both ionic conductivity and mechanical robustness of hydrogel networks. On the other hand, POMs can act as active electrochemical mediators that directly participate in signal transduction and amplification processes during biosensing.

It should be noted that the high negative charge density of POMs facilitates their interactions with proteins such as serum albumin under physiological conditions [192]. Studies have shown that the binding constant between Keggin-type POMs (e.g., $[H_2W_{12}O_{40}]^{6-}$) and human serum albumin (HSA) can reach the order of 10^6 M^{-1} [193]. Moreover, upon binding with HSA, Eu-Keggin POMs exhibit a decrease in the number of coordinated water molecules from four to zero, indicating direct coordination interactions between POMs and protein surfaces. These POM–protein interactions have dual implications for biomedical applications. On the one hand, the specific binding of POMs to certain proteins may contribute to their therapeutic activity at the molecular level. On the other hand, nonspecific protein adsorption may induce the formation of a "protein corona," thereby altering the in vivo distribution, cellular uptake, and biological activity of POMs [194]. Within hydrogel matrices, the three-dimensional polymer networks can partially restrict POM diffusion and exposure, thereby reducing the risk of nonspecific protein adsorption. However, the effectiveness of this protective effect depends on the crosslinking density, POM anchoring strategy, and specific physiological environment.

With respect to ionic conductance enhancement and mechanical sensing, Ma *et al* [33] developed an ionically conductive hydrogel by incorporating a lanthanide-based POM (EuW_{10}) and an ionic liquid into a polyacrylamide network. Strong interactions between the multicharged POM clusters and ionic liquid cations not only reinforce the network through physical crosslinking but also promote the formation of ordered ion-transport pathways. As a result, the hydrogel exhibits high ionic conductivity (~11.22 mS cm^{-1}) and excellent strain-sensing performance, enabling stable and sensitive monitoring of human motion. This work demonstrates how POMs can simultaneously contribute to mechanical integrity, ionic transport, and multifunctional sensing capabilities.

More distinctive applications arise from exploiting the redox activity of POMs for highly sensitive biochemical sensing [59, 195]. Chen *et al.* [79] reported POM-gated organic photoelectrochemical transistors in which POMs embedded within the hydrogel gate layer serve as the central elements for signal conversion and amplification. The reversible multi-electron redox behavior and efficient light-harvesting capability of POMs enable the transduction of weak chemical or optical stimuli into pronounced changes in transistor channel current. This architecture effectively bridges soft biointerfaces

with solid-state electronics, establishing a new paradigm for real-time, highly sensitive detection of physiologically relevant analytes such as neurotransmitters and glucose in complex biological environments (Figure 6 B). Despite the unique advantages of POMs in bioelectronics, this field remains at an early stage, with several fundamental issues requiring further investigation. The long-term electrochemical stability of POMs under continuous hydration and repeated redox cycling conditions remains unclear, as structural fatigue or irreversible degradation may substantially shorten the operational lifetime of devices [196]. Meanwhile, the effects of POM network rearrangement during dynamic deformation of hydrogels (e.g., stretching and bending) on interfacial impedance and signal fidelity have not been systematically investigated. More fundamentally, nonspecific interactions between POMs and proteins are particularly critical at sensing interfaces. In complex biological fluids, such as serum or interstitial fluid, the formation of a protein corona may shield the active sites of POMs, resulting in reduced sensitivity or signal drift. Addressing this issue is essential for ensuring the reliability of POM-based sensors under realistic physiological conditions.

Looking ahead, research in this area is expected to focus on the development of multifunctional, integrated sensing patches capable of synchronous monitoring and wireless transmission of multiple physiological parameters. In parallel, efforts will be directed toward engineering POM-based hydrogel electrodes with improved biocompatibility, enhanced interfacial stability, and reduced impedance, thereby facilitating the realization of long-term, reliable, and safe implantable bioelectronic systems.

In summary, POM-based hydrogels have demonstrated broad potential in wound healing, antimicrobial therapy, cancer treatment, and bioelectronics. Their versatility arises from the integration of the unique chemistry of POMs with the biocompatibility and mechanical adaptability of polymer networks. Collectively, these advances represent a paradigm shift in biomaterial design, transforming hydrogels from passive carriers into active, responsive therapeutic and diagnostic platforms. Future research is expected to improve the intelligent responsiveness of POM-based hydrogels to pathological microenvironments and enhance the spatiotemporal coordination of multiple therapeutic modalities, including catalytic therapy, immunomodulation, and electrical stimulation. These advances will further facilitate the clinical translation of multifunctional POM-based hydrogel systems for precision medicine.

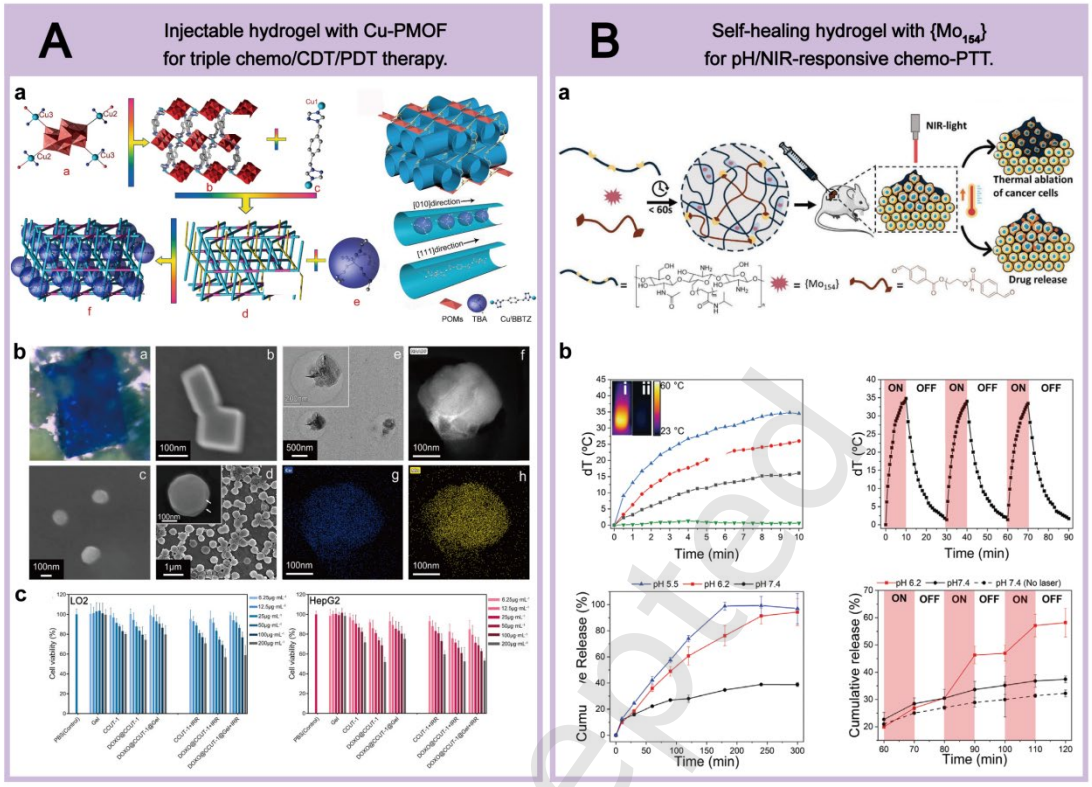

Figure 6 Polyoxometalate-Based Hybrid Hydrogels for Biomedical Therapy and Bioelectronic Applications. (A) Dual-crosslinked dynamic hydrogel incorporating {Mo_{154}} wheel-shaped polyoxometalate for pH/NIR dual-responsive chemo-photothermal therapy. (a) Schematic illustration. (b) Structural and morphological characterization. (c) Biocompatibility testing. (B) POM-gated organic photoelectrochemical transistor. (a) Schematic illustration. (b) Performance curves of the transistor. (A) is reprinted with permission from Ref. [78], Advanced Materials. 2021. (B) is reprinted with permission from Ref. [79], Advanced Functional Materials. 2024.

3.5 Comparison of Key Parameters in Representative Studies

To facilitate a systematic comparison of the technical parameters and performance characteristics of representative studies across different application areas, Table 2 summarizes the key indicators of POM-based hydrogel systems, including POM type, polymer matrix, crosslinking method, POM leaching behavior, in vivo stability, and reported toxicity.

Table 2. Comparison of key parameters in representative studies of POM-based hydrogels

application areas	POM type	polymer matrix	Crosslinking method	Leaching %	in vivo stability	reported toxicity
Wound healing and tissue repair	Preyssler [72]	Fibrin/ GelMA	*In situ* hierarchical crosslinking combined with hydrogen bonding	<5% in Na^+-free physiological buffer; rapid Na^+-responsive release	Stable retention over 7 days in rat infectious wound model	No obvious cytotoxicity; hemolysis rate <5%; no systemic organ damage
	Manganese-based polyoxometalate (MnPOM) nanozyme [155]	Gelatin-polyacrylamide (GPP)	Free radical polymerization with liposome-mediated physical encapsulation	~32% cumulative release over 14 days (sustained profile)	Stable therapeutic effect for 10 days in diabetic rat wound model	Low cytotoxicity; no detectable organ damage in vivo
	Keggin [141]	Polyaniline/ hyaluronic acid supramolecular hydrogel	Supramolecular self-assembly via hydrogen bonding and π-π stacking	~26% cumulative leaching over 7 days under physiological conditions	Stable retention and conductivity over 10 days in diabetic mouse wounds	Excellent cytocompatibility; no systemic toxicity or inflammatory response

	Zinc-based polyoxometalate (Zn-POM) nanozyme [148]	Aldehyde-methacrylic anhydride hyaluronic acid (AHAMA)	Dual crosslinking of Schiff base reaction and free radical polymerization	~28% cumulative leaching over 7 days	Stable retention over 7 days in diabetic mouse wound model	Excellent biocompatibility; no systemic toxicity in vivo
Antimicrobial and anti-biofilm therapy	Keggin-type [70]	Guanosine monophosphate (GMP) supramolecular network	Supramolecular self-assembly driven by hydrogen bonding and electrostatic interaction	<12% cumulative leaching over 7 days in PBS (pH 7.4)	Stable antibiofilm performance; mechanically robust under physiological conditions	Enhanced biocompatibility compared with free POM; low hemolysis rate
Cancer treatment and combination treatment platforms	Wheel-shaped $\{Mo_{154}\}$ polyoxometalate [78]	Benzaldehyde-PEG / PNIPAM-grafted chitosan	Dual crosslinking of Schiff base reaction and electrostatic interaction	<13% under physiological conditions; pH/NIR dual-responsive rapid release	Self-healing in vivo; stable retention for 5 days after intratumoral injection	No systemic toxicity via local administration; minimal normal tissue damage
	Wells-Dawson type $[P_2W_{15}O_{56}]^{12-}$ [75]	Carboxymethyl chitosan (CMC)	Electrostatic interaction with pH-responsive swelling behavior	~41% cumulative release over 10 days (sustained release)	Stable retention over 7 days after intratumoral injection; biodegradable	No systemic toxicity; negligible damage to normal tissues

	Tungsten-based polyoxometalate (W-POM) nanozyme [175]	Hyaluronic acid-dopamine (HA-DOPA)	Catechol oxidation crosslinking with disulfide-responsive dynamic bonds	<10% in normal tissue; GSH-responsive rapid release in tumor microenvironment	Sustained cascade catalytic activity for 14 days in tumor tissue	Low systemic toxicity; tumor-specific killing effect
	Phosphotungstate polyoxometalate (ROS scavenger) [197]	Poly-glutamic acid/ poly-lysine coacervate	Physical crosslinking via electrostatic interaction	~35% cumulative release over 14 days	Stable peritumoral retention; anti-metastasis effect lasts 21 days	High biocompatibility; no immunotoxicity or systemic damage
Bioelectronic and physiological sensing	All-inorganic isopolyoxometalate clusters [198]	Polymer-free all-inorganic supramolecular framework	Hofmeister-electrostatic synergy driven 1D supramolecular polymerization	<7% cumulative leaching over 30 days under ambient conditions	Ultra-stable proton conduction (-20~80 °C); long-cycle operational stability	No organic components; excellent chemical/thermal stability; negligible biological toxicity

4. Summary, Challenges and Prospects

POM-based hydrogels, as a class of organic–inorganic hybrid materials with programmable structure and function, have demonstrated significant potential to evolve from passive drug carriers into active platforms for diagnosis and therapy in biomedical applications [19, 22]. In this review, we systematically discuss the rational design principles governing POM-based hydrogel construction and elucidate how property customization can be achieved through polymer matrix engineering, precise functional tailoring of POM clusters, and intelligently designed interfacial crosslinking strategies. Furthermore, we provide an in-depth analysis of the underlying mechanisms and recent progress of POM-based hydrogels in key biomedical fields, including wound healing, anti-infective therapy, synergistic cancer treatment, and bioelectronic interfaces.

Despite these advances, the translation of POM-based hydrogels toward clinical practice remains confronted with a series of multidimensional challenges arising from their compositional and structural complexity [22, 199]. These challenges span several critical aspects, including long-term biosafety and biodegradability, the balance between functional performance and material stability, incomplete understanding of structure–activity–biological response relationships, and difficulties associated with scalable synthesis, reproducibility, and manufacturing standardization [200, 201]. Addressing these issues requires not only incremental material optimization but also a systematic and mechanistic understanding that bridges chemistry, materials science, and biomedical engineering.

On the basis of the comprehensive discussion presented throughout this review, this section will critically analyze the most pressing challenges currently faced by POM-based hydrogel systems and, accordingly, outline forward-looking perspectives and research directions aimed at accelerating their maturation from laboratory concepts to clinically viable biomaterial platforms.

4.1 Long-term biosafety and in vivo fate regulation

As exogenous inorganic metal–oxygen clusters, the long-term biosafety of polyoxometalates in physiological environments constitutes a fundamental prerequisite for their clinical translation [84, 202]. To date, most studies remain confined to in vitro cytotoxicity assays or short-term biocompatibility

evaluations, while comprehensive and systematic investigations into their in vivo behavior—including systemic toxicity, biodistribution, metabolic pathways, and long-term retention—are still markedly insufficient. The unresolved scientific questions in this area can be broadly categorized into three interrelated dimensions. First, the chemical stability and degradation kinetics of POMs under complex physiological conditions, particularly within acidic intracellular compartments such as lysosomes, remain poorly understood [203]. It should be noted that the stability of POMs under physiological conditions is not governed by a single mechanism but is highly dependent on their structural characteristics and constituent elements [204]. Tungsten-based Keggin-type POMs (e.g., $[PW_{12}O_{40}]^{3-}$) exhibit relatively high stability under near-neutral pH conditions, whereas molybdenum-based analogues (e.g., $[PMo_{12}O_{40}]^{3-}$) undergo significant hydrolysis at pH values above 4 – 5. Although hydrogel encapsulation can delay this degradation process, it cannot completely prevent it [205]. This limitation becomes particularly evident in acidic environments, such as lysosomal compartments (pH ~4.5 – 5.0) or inflammatory microenvironments, where POM degradation can be substantially accelerated. It is still unclear whether POM frameworks undergo partial or complete decomposition into free metal species, including molybdenum, tungsten, or vanadium ions, and how such processes may lead to organ-specific accumulation and potential chronic toxicities, such as the reported neurotoxicity associated with vanadium ions. Furthermore, whether hydrogel networks truly protect POM clusters from degradation or merely enable the controlled release of POM degradation products is a fundamental distinction with significant implications for long-term safety assessment [31]. The degradation products derived from different POM structures, including tungstates, molybdates, and vanadates, possess distinct toxicological profiles and therefore require case-by-case evaluation rather than generalized assumptions. Second, the therapeutic window of POM-mediated biological activity is often intrinsically narrow [89, 167, 206]. The local concentrations required to achieve effective antimicrobial, catalytic, or electrochemical performance may approach or even exceed the tolerance thresholds of normal cells, thereby increasing the risk of off-target effects and limiting clinical safety margins. Third, the interactions between POMs or their degradation products and the immune system have not been sufficiently elucidated [207, 208]. Inadequate understanding of these interactions raises concerns regarding unintended immunogenicity, aberrant inflammatory activation, or disruption of immune microenvironment homeostasis, which are particularly critical for long-term applications such as tissue regeneration scaffolds and implantable bioelectronic devices.

Addressing these challenges will require the integration of advanced tracing technologies, including radioactive or stable isotope labeling and high-resolution in vivo imaging, with systematic toxicological and pharmacological approaches [209, 210]. Such combined methodologies are essential to quantitatively map the complete pharmacokinetic and pharmacodynamic profiles of POMs and their metabolites in relevant disease models. In parallel, increasing attention should be devoted to active regulation of the in vivo fate of POMs through rational surface engineering strategies, such as biocompatible coatings, biodegradable encapsulation, or targeted ligand modification. These approaches offer viable pathways to modulate biodistribution, metabolism, and clearance behavior, thereby establishing a robust safety foundation for the future biomedical application of POM-based hydrogel systems.

4.2 Synergistic optimization of functional activity and structural stability

An inherent design dilemma exists in POM-based hydrogel systems, arising from the competing requirements of functional activation and structural stabilization [22]. On the one hand, the full expression of POM-mediated bioactivity relies on sufficient exposure and accessibility of their catalytically active sites to biological substrates such as hydrogen peroxide, dissolved oxygen, or specific ions within the pathological microenvironment [206, 211]. On the other hand, long-term material stability, durability, and biosafety demand that POMs be effectively immobilized within the polymer network to prevent premature leakage, preserve network integrity, and enable controlled release kinetics [212, 213]. Although non-covalent immobilization strategies—most notably electrostatic interactions—are currently predominant due to their mild conditions and operational simplicity, the strength of these interactions is highly sensitive to variations in ionic strength and pH. In complex physiological fluids, competitive ion binding can readily weaken electrostatic cross-links, leading to network dissociation or burst release of POMs, thereby limiting their suitability for applications such as long-term implantation.

Conversely, covalent fixation strategies can substantially enhance the structural stability and retention of POMs [27, 56, 214]; However, excessively rigid covalent linkages may restrict the conformational adaptability of POM clusters, impede substrate diffusion, or partially shield active sites, ultimately compromising their intrinsic catalytic or redox activity [204]. Resolving this contradiction requires

moving beyond the paradigm of static immobilization toward the development of intelligent and responsive dynamic anchoring strategies. One promising approach involves the rational design of stimulus-responsive linker arms or crosslinking motifs that remain stable under physiological homeostasis but undergo controlled cleavage or conformational transitions in response to pathological cues, such as overexpressed enzymes, aberrant pH, or elevated reactive oxygen species levels [215, 216]. Such stimulus-adaptive anchoring mechanisms enable spatiotemporally regulated activation of POM functionality, shifting material behavior from an "always-on" mode to a precisely controlled, on-demand therapeutic response.

In parallel, multiscale structural engineering of the hydrogel network itself provides an additional avenue for synergistic optimization. Fine-tuning parameters such as pore size distribution, pore interconnectivity, and the balance between hydrophilicity and hydrophobicity can enhance the physical confinement of POMs while simultaneously maximizing their accessibility to target substrates [217, 218]. Through the coordinated optimization of chemical immobilization strategies and network architecture, it becomes possible to reconcile functional efficiency with structural robustness, thereby advancing POM-based hydrogels toward more reliable and application-specific biomedical platforms.

4.3 Deep correlation between macroscopic properties and microscopic molecular mechanisms

Current evaluations of the biological performance of POM-based hydrogels are predominantly centered on macroscopic phenotypic endpoints, including antibacterial inhibition zone size, wound closure rates, and tumor volume reduction, typically supplemented by basic cellular assays such as proliferation, migration, or apoptosis [22, 169]. While these metrics provide essential proof-of-concept validation, they offer limited insight into the underlying molecular and cellular mechanisms by which POMs exert their biological effects. In particular, how POMs precisely regulate complex cellular behaviors—such as macrophage polarization, stem cell fate determination, tumor cell death modality selection, or endothelial angiogenic signaling—through their distinctive redox activity, catalytic cycling, and ion exchange capabilities remains insufficiently understood and largely fragmented [219].

A representative example lies in the role of reactive oxygen species generated by POMs. At low and tightly regulated concentrations, ROS can function as secondary messengers that activate pro-

regenerative signaling pathways and promote cell migration and tissue repair [220-222]. In contrast, excessive ROS accumulation can induce oxidative stress, mitochondrial dysfunction, and programmed cell death [223-225]. The molecular basis of this dose-dependent biphasic effect, including the precise thresholds and the downstream signaling networks involved—such as NF-κB, MAPK, Nrf2, and related redox-sensitive pathways—has yet to be systematically elucidated. As shown in Figure 7 drawn by Figdraw, following endocytic uptake, POM clusters may undergo endosomal escape or lysosomal entrapment. Depending on their stability and local pH, they may degrade and release metal species that target mitochondria, lysosomes, or the nucleus. These events collectively determine downstream outcomes including apoptosis, ferroptosis, and immune modulation. Elucidating this intracellular trajectory is therefore critical for establishing robust structure-activity relationships. In the absence of such mechanistic clarity, material performance optimization remains largely empirical, relying on trial-and-error approaches that hinder true rational design and targeted functional enhancement.

Addressing this challenge will require a paradigm shift toward mechanism-driven research strategies. Future studies should integrate multi-omics approaches, including transcriptomics, proteomics, and metabolomics, with high spatiotemporal-resolution in situ imaging and the development of specific molecular probes capable of tracking redox dynamics, ion fluxes, and catalytic intermediates in real time [226, 227]. Through such integrated methodologies, it will become possible to systematically decode the complete cascade by which “material-derived signals” are sensed by cells, transduced through intracellular signaling networks, and ultimately translated into specific biological outcomes. Beyond providing a robust theoretical foundation and predictive framework for biosafety assessment and functional optimization, this mechanistic understanding may also uncover previously unrecognized biological activities of POMs, thereby opening new and unexplored frontiers for their biomedical application.

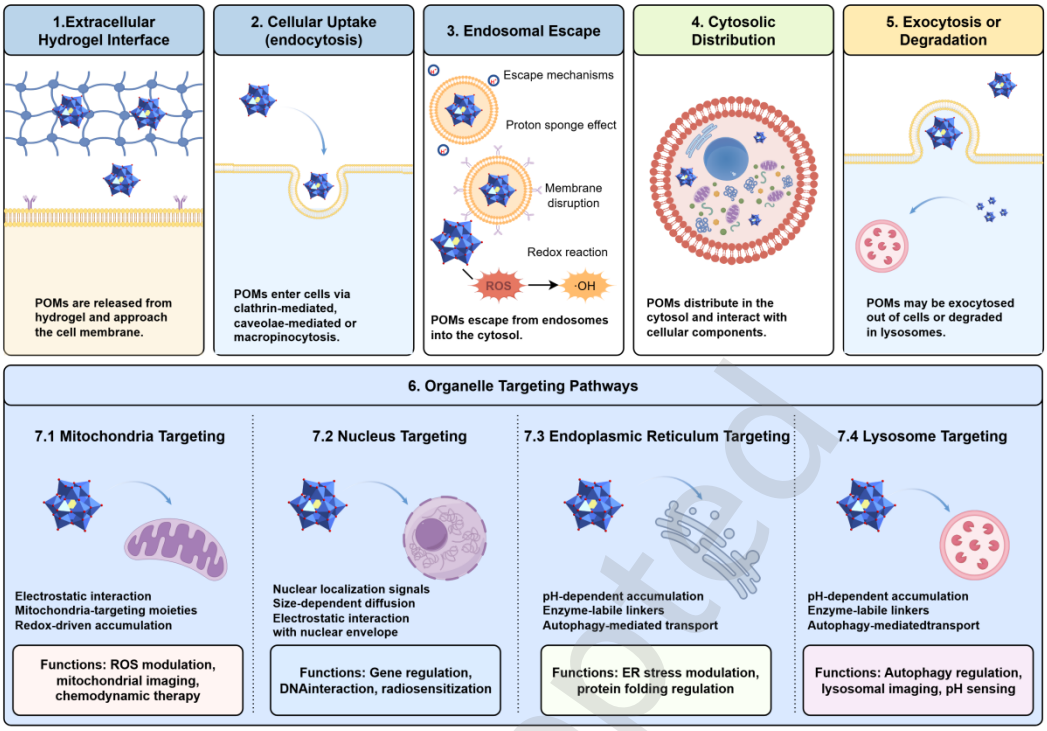

Figure 7. Schematic illustration of the intracellular fate of POMs: endocytosis, endosomal escape, organelle targeting, and resulting biological outcomes.

4.4 Practical barriers to large-scale preparation and clinical translation

Translating POM-based hydrogels from milligram- or gram-scale laboratory preparations to kilogram-scale production suitable for preclinical evaluation and eventual clinical trials presents substantial challenges in process engineering and manufacturing control. The synthesis and purification of POMs typically require stringent regulation of reaction parameters, multistep separation procedures, and highly specific crystallization conditions, all of which complicate scale-up while maintaining structural fidelity and batch-to-batch consistency. During large-scale compounding of POMs with polymer monomers or prepolymers, achieving homogeneous nanoscale dispersion, preventing cluster agglomeration, and precisely regulating subsequent crosslinking reactions to form reproducible three-dimensional networks represent critical technical bottlenecks [228].

Beyond manufacturing, terminal sterilization—an essential requirement for clinical use—poses additional risks [229]. Common sterilization methods for medical devices and biomaterials, including γ-irradiation, ethylene oxide exposure, and steam autoclaving, may irreversibly alter the physical

architecture of hydrogels through network degradation or abnormal swelling, while simultaneously affecting the chemical integrity of POMs by inducing changes in oxidation state, cluster dissociation, or loss of catalytic activity [230, 231]. Preserving both structural integrity and functional performance under clinically acceptable sterilization conditions therefore remains a nontrivial challenge that must be addressed early in material design.

From a regulatory and translational perspective, POM-based hydrogels occupy an ambiguous position as innovative organic–inorganic hybrid systems, for which there is currently no well-established regulatory precedent or unified classification framework. Depending on their intended use and mode of action, such materials may be regulated as medical devices, drugs, or combination products, each pathway imposing distinct evaluation criteria and approval requirements across different jurisdictions. This uncertainty underscores the necessity for early and proactive engagement with regulatory authorities and for the prospective design of comprehensive non-clinical development programs. These programs should encompass chemistry, manufacturing, and control (CMC) considerations, alongside systematic pharmacological, toxicological, and biocompatibility assessments, with reference to existing guidelines for nanomedicines, tissue-engineered medical products, or drug-device combination systems. Only through the generation of a rigorous and integrated data package can POM-based hydrogels progress from promising laboratory innovations to clinically viable biomedical platforms.

4.5 Future prospective directions and interdisciplinary integration

Realizing these visions requires fundamental advances in both material design paradigms and manufacturing technologies. The integration of emerging technologies, including artificial intelligence (AI), microfluidics, additive manufacturing, and bioelectronics, is providing unprecedented opportunities to accelerate the transition of POM-based hydrogels from laboratory discoveries toward clinical translation.

In terms of material design and prediction, the incorporation of machine learning is fundamentally reshaping the discovery paradigm of POM-based materials [232]. Traditional exploration of POM synthesis relies heavily on extensive trial-and-error experiments, which are inefficient and difficult to comprehensively navigate the vast chemical space. In recent years, various data-driven approaches have

been developed to accelerate this process. Machine learning algorithms have been successfully integrated with robotic synthesis platforms to enable closed-loop exploration of the chemical space of POM-based framework materials [233] . In biomedical applications, AI can further assist in predicting the cytotoxicity, biodistribution, and metabolic pathways of POMs, allowing candidate structures with improved safety profiles to be identified before synthesis [234]. With the accumulation of high-quality POM datasets, including physicochemical properties and biological activity data, and the implementation of FAIR data principles, AI is expected to evolve from an auxiliary tool into a central driver for POM-based hydrogel design.

Microfluidic technology provides a precise platform for the high-throughput synthesis and screening of POM-based hydrogels [235]. Droplet-based microfluidics enables accurate control over reaction conditions at the microscale and automated execution of large numbers of parallel experiments [236]. For POM systems, microfluidic reactors have been applied to POM synthesis and the fabrication of POM-based microfluidic devices [237]. The major advantages of this strategy are twofold. First, it can substantially reduce the consumption of valuable POM precursors. Second, it enables rapid screening of combinations of different POM structures, polymer matrices, and crosslinking conditions under highly controlled and reproducible conditions, thereby facilitating the identification of optimal formulations. Furthermore, microfluidic platforms can incorporate online analytical modules to provide real-time feedback on the structure and performance of synthesized materials, further accelerating iterative material optimization.

Additive manufacturing (3D/4D printing) opens new possibilities for the structural customization of POM-based hydrogels [238, 239]. Conventional casting or injection molding approaches are generally limited in constructing complex geometries and internal architectures, whereas 3D printing extends the design freedom of POM hydrogels from material composition to macroscopic structural organization [240]. In biomedical contexts, this capability enables the fabrication of hydrogel scaffolds with precisely tailored dimensions, porosity, and mechanical gradients for different patients or anatomical sites, providing opportunities for personalized therapeutic strategies. Meanwhile, 4D printing, in which 3D-printed structures undergo programmed shape or functional changes in response to external stimuli (e.g., temperature, pH, or light), introduces an additional dimension to the intelligent responsiveness of POM-

based hydrogels.

For wearable and implantable devices, the ionic conductivity, redox activity, and biocompatibility of POM-based hydrogels make them promising candidates for physiological monitoring applications [241]. Recent studies have integrated POM-based hydrogels into flexible strain sensors for real-time monitoring of joint movements, including finger, wrist, and elbow motions. Some systems also exhibit antibacterial properties, providing potential solutions to infection-related challenges associated with long-term wearable device use [241]. For future implantable applications, key challenges include maintaining stable interfacial impedance and signal fidelity under dynamic deformation, as well as minimizing the interference of nonspecific protein adsorption with sensing sensitivity.

The integration of these four technological strategies—AI-driven rational design, microfluidics-enabled high-throughput screening, additive manufacturing-assisted personalized fabrication, and bioelectronics-supported real-time functional monitoring—will establish a comprehensive closed-loop development paradigm [242]. In this framework, AI predicts optimal structures, microfluidics rapidly validates and optimizes material formulations, 3D printing enables the fabrication of optimized materials into functional architectures, and bioelectronic devices provide real-time feedback on in vivo performance [243]. These feedback data can subsequently be incorporated into AI models to guide the next generation of material design. Such a closed-loop strategy is expected to significantly shorten the pathway from proof-of-concept studies to preclinical evaluation of POM-based hydrogels, thereby facilitating their eventual clinical translation and commercialization.

Ultimately, realizing this vision requires substantial progress in several fundamental scientific challenges. The actual physicochemical state of POMs under physiological conditions—including their hydration state, counterion exchange behavior, and intercluster aggregation—remains poorly understood because of the lack of systematic in situ characterization. Consequently, the biological activities of POMs are often interpreted based on simplified assumptions. Establishing quantitative structure–activity relationships between POM structures and specific biological effects should replace the current trial-and-error approach to material discovery. Systematic comparisons of how different crosslinking strategies influence the redox potential of POMs, substrate diffusion, and long-term catalytic stability are also

needed to improve the predictability of material design. From a translational perspective, localized delivery systems, such as postoperative coatings, periodontal membranes, and chronic wound dressings, are likely to reach clinical evaluation earlier than systemic or long-term implantable platforms because of their lower systemic exposure and more practical regulatory pathway. Ultimately, progress in this field will depend on shared databases, standardized evaluation protocols, and interdisciplinary collaboration spanning chemistry, materials science, and clinical medicine.

In summary, the field of POM-based hydrogels is currently at a critical juncture, transitioning from vibrant fundamental research toward application-driven development with tangible clinical relevance. Future success will depend not only on continued advances in materials chemistry and syntheticmethodologies, but also on a deep mechanistic understanding of bio-material interactions, systematicsolutions to translational challenges, and the active implementation of interdisciplinary collaborativemodels. Through sustained efforts in mechanism-driven research, rational material design, and cross-disciplinary cooperation, POM-based hydrogels are expected to evolve from promising multifunctional concepts into reliable biomedical technologies capable of addressing unmet clinical needs and advancing the frontiers of precision medicine and advanced biomaterials.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contributions

T.Q.L was involved in conceptualization, investigation, and original draft writing. J.Q.Z contributed

tomethodology, investigation, and writing. H.Y.Q was involved in investigation, review, and writing. L.Wcontributed to conceptualization and funding acquisition. J.M contributed to conceptualization andfunding acquisition. X.Q.X was involved in conceptualization, review and editing, project administration,and funding acquisition.

Use of AI statement

None.

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Graphical abstract