Metal–Organic Framework-Based Nanozymes

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Contributor: Anupriya Baranwal, Shakil Ahmed Polash, Vijay Kumar Aralappanavar, Bijay Kumar Behera, Vipul Bansal, Ravi Shukla

A nanozyme is a nanoscale material having enzyme-like properties. It exhibits several superior properties, including low preparation cost, robust catalytic activity, and long-term storage at ambient temperatures. Moreover, high stability enables repetitive use in multiple catalytic reactions. Hence, it is considered a potential replacement for natural enzymes. Enormous research interest in nanozymes has made it imperative to look for better enzyme-mimicking materials for biomedical applications. Given this, research on metal–organic frameworks (MOFs) as a potential nanozyme material has gained momentum. MOFs are advanced hybrid materials made of inorganic metal ions and organic ligands. Their distinct composition, adaptable pore size, structural diversity, and ease in the tunability of physicochemical properties enable MOFs to mimic enzyme-like activities and act as promising nanozyme candidates.

Keywords: metal–organic framework ; MOF ; nanozyme ; enzyme-mimic ; biosensor ; therapeutics ; cancer therapy ; antimicrobial ; anti-inflammatory

1. Introduction

Enzymes are naturally occurring biological catalysts that accelerate the rate of biochemical reactions without being consumed in the process. They are almost always proteins and only sometimes RNA (ribozymes). As strong biological catalysts, natural enzymes exhibit high catalytic activity and substrate specificity, enabling them to be applied in fields including, but not limited to, bioengineering, food processing, biomedicine, chemical production, and environmental remediation [1][2][3]. Despite these promising merits, natural enzymes suffer from intrinsic limitations of cumbersome preparation, complex and expensive purification, low recyclability, difficult tunability, and poor stability. Given this, extensive efforts have been made to develop artificial enzymes that can overcome these shortcomings and replace natural enzymes [4][5][6]. Ever since the discovery of magnetic nanoparticles with intrinsic peroxidase (POX)-like activity [7], various nanomaterials such as metal and metal oxide nanoparticles, metal–organic frameworks (MOFs), carbon nanomaterials, and their composites have been investigated for enzyme-like activities [8][9][10][11][12][13][14][15]. These enzymes mimicking catalytic nanomaterials are being referred to as ‘nanozymes’ by following a similar nomenclature pattern as that of DNAzymes, ribozymes, synzymes, etc. Unlike natural enzymes and other conventional artificial enzymes, nanozymes can be easily synthesized and mass-produced at a lower cost.

Moreover, the unique physicochemical properties of nanozymes endow them with an ease of tunability, high catalytic activity and stability, and longer shelf-life [11][16]. These merits and advancements in nano-biotechnology have pushed nanozymes to the forefront of developing new biosensors, theranostics, bioimaging techniques, antimicrobials, and environmental treatments [17][18][19][20][21]. Despite achieving such commendable progress in a relatively short span, only certain nanozymes can perform efficiently *in vitro* catalysis. In contrast, others show inadequate performance and poor catalytic reaction selectivity due to the influencing intrinsic (pH, temperature, redox condition, and oxygen level) or extrinsic (light, magnetic field, heat, and ultrasound) parameters [22][23][24]. In addition, several other factors, such as the size, morphology, elemental composition, surface modification, and crystal structure of nanozymes, could also influence their catalytic performance [22]. Therefore, it is imperative to develop nanozymes with precise catalytic mechanisms and active sites to meet the standards of natural enzymes and broaden their scope of biomedical applications [25][26].

MOFs are an emerging class of porous, crystalline, inorganic–organic hybrid materials that consist of coordinated metal ions/clusters (metal nodes) and organic ligands [27][28][29]. Owing to the strong coordination between metal nodes and bridging ligands, MOFs with unique structures and flexible properties have emerged. These include the presence of (i) molecular/atomic level catalytic sites, (ii) multiple channels and ultrahigh porosity, (iii) abundant catalytic active sites, (iv) synthesis and chemical tunability, and (v) high stability [30][31][32][33]. On account of these properties, MOFs have been applied in fields ranging from chemical catalysis, biochemical analysis, sensing, energy storage, gas separation, antimicrobials, drug and gene delivery, and so on [34][35][36][37][38][39]. In recent years, MOFs have become promising candidates in bio-catalysis due to their intrinsic nanozyme activity and ability to facilitate enzyme immobilization [34][40].

Compared to traditional nanozymes, MOF-NZs possess the potential to create a diverse range of nanozymes due to the versatility of metal ions and organic linkers. Their regularly arranged unit cells offer active catalytic sites with improved enzyme mimicry, and their porous structure aids in directing substrates to these active sites [41]. Moreover, the modular nature of MOFs promotes the incorporation of various metal ions or clusters, allowing for precise control over catalytic properties [42]. By combining the therapeutic and catalytic functionalities in a single material, MOFs can also serve as excellent drug delivery carriers and play a crucial role in theranostics [43]. Owing to this, different types of MOFs, including unmodified/pristine MOFs, modified MOFs, derived MOFs, and MOFs conjugated with natural enzymes, have been investigated for their nanozyme activity [24][44][45]. Reportedly, pristine MOFs, such as Material Institute of Lavoisier (MIL)-53, MIL-88, MIL-100, and MIL-10, can exhibit excellent catalytic activity by either mimicking the natural enzymes' active sites or by polyvalent elements [46]. Their modified forms have been developed to add chemical functionality to the MOF interior or onto its surface by using metal [47][48] and metal oxide [47][48] nanoparticles. To further improve the catalytic activity of MOFs, their derivatives have been synthesized by employing thermolysis [49], etching [50], or pyrolysis methods [51]. In addition to this, MOF-encapsulated natural enzymes have been prepared to increase their stability under harsh conditions and exhibit superior catalytic activity than that of pristine MOFs [52][53]. Thanks to the diversity and structural tunability of MOF-based materials, MOF-based nanozymes (MOF-NZs) simulating a variety of enzyme-like activities have been developed and applied in various biomedical fields (**Figure 1**).

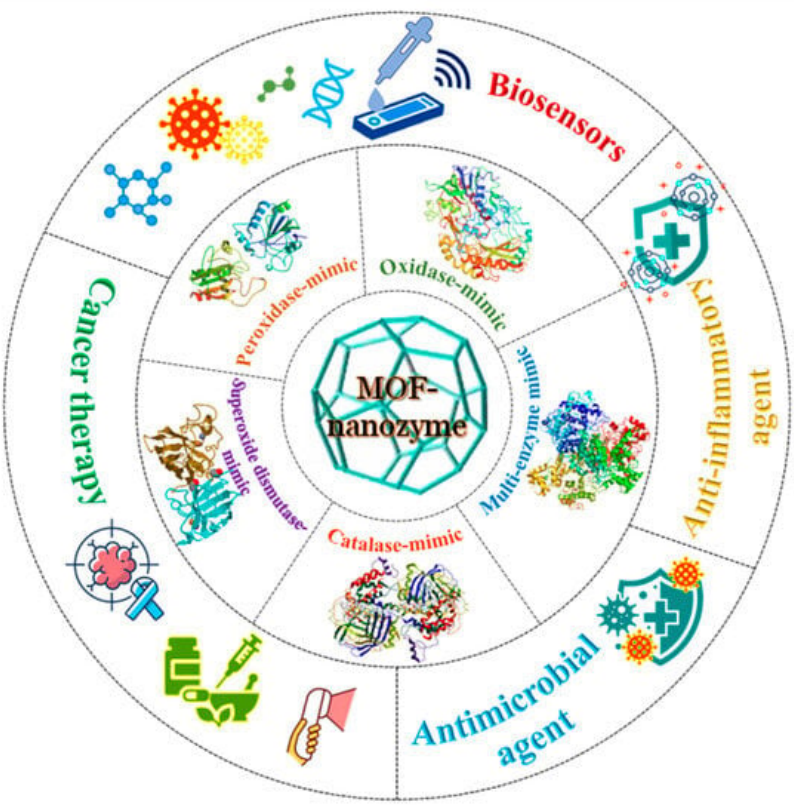

Figure 1. Schematic illustration summarizing types of MOF-NZs and their potential applications in various biomedical fields.

2. Types of MOF-NZs

MOF-NZs exhibit high catalytic activity compared to that of pristine nanozymes due to their structural components: metal nodes (e.g., Fe, Cu, Ce, Mn, etc.) and organic ligands (e.g., 2-methyl imidazole, 2,2′-dithiosalicylic acid, etc.) [54], where the former acts as a redox couple (e.g., Fe^{3+}/Fe^{2+}, Cu^{2+}/Cu, Ce^{4+}/Ce^{3+}, Mn^{2+}/Mn) and the latter acts as a redox mediator for donating and accepting electrons from one substrate to another [55]. Over the last few years, numerous MOFs have been successfully developed to mimic the peroxidase (POX), oxidase (OX), superoxide dismutase (SOD), and catalase (CAT) activities of natural enzymes. Interestingly, some of the developed MOFs could also mimic two or more enzymatic activities under the same conditions or in a different environment. The following section is compiled to summarize different types of MOF-NZs reported in recent years.

2.1. Peroxidase-Mimic

POX is an oxidoreductase enzyme that catalyzes the oxidation of substrates by employing peroxide as an electron acceptor. POX activity is mainly attributed to Fenton-reactions, wherein the chromogenic substrates, such as 3,3′,5,5′-tetramethylbenzidine (TMB), 2,2-azinobis(3-ethylbenzothiazoline)-6-sulfonic acid (ABTS), and o-phenylenediamine (OPD)

(electron donors), are oxidized in the presence of H_2O_2 (electron acceptor). A natural POX such as horse-radish peroxidase (HRP) has a coordinated heme molecule that serves as a catalytic active site. To mimic the structural and functional attributes of HRP, MOFs have been developed with a hybrid array of central metal nodes acting as active catalytic sites, and organic linkers as structural ligands [6]. For example, in iron-porphyrin MOFs, the iron-porphyrin structure is employed as a structural motif to mimic the heme-like active center and function as a POX [56].

2.1.1. Pristine MOF Nanozymes

To date, numerous MOFs containing active redox couples as metal nodes have been developed to mimic the POX activity. To date, several MOFs have been reported to show intrinsic peroxidase-mimic activity, such as Material Institute of Lavoisier (MIL)-53 (20), MIL-100(Fe) (21), MIL-100(Al)-NH_2 (19), and Hong Kong University of Science and Technology (HKUST)-1 [57]. These redox couples catalytically activate H_2O_2 by employing a Fenton-like reaction to produce a hydroxyl radical ($^{\bullet}OH$) and thus render MOFs to oxidize chromogenic POX substrates [58][59]. In one such report, Cu(II)-MOFs were designed using 4,4′-bipyridine as organic linkers and Cu(II) as the active metallic center by employing a self-assembly strategy [59]. The Cu(II) metal nodes acted as a POX-mimic and oxidized the chromogenic substrate ABTS in the presence of H_2O_2. Moreover, the positively charged Cu(II)-MOF showed a higher electrostatic affinity towards electronegative ABTS (lower K_m) than that of HRP. Similarly, MIL-68 and MIL-100 were developed with Fe(III) as an active metal catalyst using a solvothermal process, wherein both MOFs mimicked POX by oxidizing the chromogenic substrate TMB to produce a deep blue color product in the presence of H_2O_2 [60]. While these pristine MOFs have certain advantages over natural enzymes, they possess limited catalytic active sites, exhibit poor affinity and specificity to substrates, and display poor catalytic performance. This warrants a further improvement in the structural attributes of MOFs during synthesis or post-synthesis modification.

2.1.2. Modified MOF Nanozymes

Metal nodes or organic linkers of pristine MOFs are modified either during or post-synthesis to develop highly performing MOF-derived nanozymes [6]. There are various means to achieve MOF derivatives: (i) metal ions substitution/exchange, (ii) heteroatom doping, (iii) organic ligand substitution, (iv) the introduction of new functional groups, (v) using MOF as a sacrificial template to develop nanomaterials with enzyme-mimic activity, and (vi) the introduction of nanoparticles. Interestingly, the combination of one or more strategies has been shown to increase the catalytic performance of MOFs through (i) structure and size modification, (ii) the addition of new recognition sites, and (iii) an increase in the number of active sites. Using the heteroatom doping strategy, Cheng et al. doped non-catalytic Ni(II) nodes into 1-D metal oxide octahedral chains of MOF-53(Fe) by using two facile procedures: solvothermal synthesis and hydrogen reduction [61]. As a result, the designed bimetallic Ni_x-Fe-MOF posed superior POX-mimic activity, increased the number of coordination unsaturated sites, and enhanced substrate affinity. Moreover, Fe(III)/Fe(II) in bimetallic Ni_x-Fe-MOF is involved in the reversible catalysis of H_2O_2. Another approach to obtaining MOF-derived nanozymes is by using MOFs as sacrificial templates under various annealing conditions. Using (ZIF)-67 as a substrate template, Chen et al. developed a Co_3O_4@CO-Fe oxide double-shelled hybrid nanocage (DSNC) by combining an anion exchange reaction between the zeolitic imidazolate framework (ZIF)-67 and $[Fe(CN)_6]^{3-}$ followed by low-temperature pyrolysis at 350 °C for 2 h [62]. On one hand, Co_3O_4 and Fe oxide rendered a derived MOF with excellent POX-like activity, and on the other hand, the Co_3O_4@CO-Fe oxide porous structure provided a confined nano-framework for substrate-catalyst reactions and additional active sites for substrate catalysis. Owing to the excellent catalytic potential of the developed MOF composite, researchers could detect H_2O_2 with high sensitivity and selectivity in the serum samples. Thus, from the aforementioned studies, it is evident that the MOF modification by heteroatom doping would be a feasible strategy to increase the overall catalytic performance and substrate specificity of the pristine MOF.

The enzyme-mimic properties of various metal/metal oxide NPs (e.g., Au, Ag, iron oxide, zinc oxide, etc.) have been explored for their wide range of applications in nanozyme-based biomedicine. However, limited structural attributes, a low catalytic performance due to inefficiently exposed active sites, and poor stability (homo-or/and hetero-aggregation) often limit their wide range of practical applications in complex natural systems [6]. To address this, MOFs with large porous structures are explored as a structural scaffold for incorporating POX-mimic metal/metal oxide NPs, which exhibited a synergistic POX-mimic catalytic activity, excellent substrate affinity, and high NP stability. Li et al. functionalized the POX-mimic activity of Pt NPs with a catalytically inert UiO-66-NH_2 MOF for the detection and removal of Hg(II) from the water samples [63]. The dispersed NPs exhibit higher POX-like activity relative to pristine Pt NPs. Moreover, the porous microstructure of the MOF increased the substrate-catalyst interaction with better catalytic activity and stability of the Pt NPs of the developed MOF. Similarly, the dispersion of Au NPs on the NH_2-MIL-125(Ti) MOF formed a multifunctional AuNPs@NH_2-MIL-125(Ti) with a higher substrate affinity and synergistic POX-mimic activity. The AuNPs@NH_2-MIL-125(Ti) demonstrated a highly sensitive and selective detection of H_2O_2, cysteine, and Hg(II) ions from the water system [64]. Dang et al. developed a bimetallic (Mn, Fe) MOF and functionalized it with gold nanoparticles (AuNPs) and anchored

carbon-nanotubes (CNTs) (Au/MOF(Fe, Mn)/CNTs) as an excellent POX-mimic [65]. The developed composite nanozyme was then employed to mediate the sensitive detection of glucose, H_2O_2, and sulfadimethoxine. The presence of Mn and Fe in an MOF composite not only increased the number of catalytic active sites but also enhanced electron transfer between MOF, Au, and CNTs, thereby resulting in a two-to-eight-times higher POX-mimic activity than that of a pristine MOF. On further analyses, the bimetallic MOF composites displayed a higher substrate affinity (K_m = 0.33 mM) and reaction velocity (V_{max} = 17.65 × 10^{-7} M s^{-1}) for H_2O_2 than that of natural HRP (K_m = 3.7 mM, V_{max} = 0.87 × 10^{-7} M s^{-1}), suggesting that a developed MOF composite could successfully serve as an HRP surrogate in biosensor platforms. Thus, the functionalization of MOFs with metal/metal oxide nanozymes resulted in synergistic POX-mimic activity with significant catalytic performance, superior surface characteristics, enhanced substrate availability and affinity, and reusability.

2.2. Oxidase-Mimic

OX-mimic nanozymes directly activate dissolved O_2 to form $^{\bullet}O_2$ radicals, preventing the use of unstable and destructive H_2O_2 as an oxidant [46]. Owing to their excellent O_2 reduction activity, the noble metal NPs and their composites have displayed OX-mimic catalytic activity [66][67]. However, their high synthesis cost and limited availability hindered their widespread application. Some of the transition metal oxide NPs, such as CeO_2 NPs, MnO_2 NPs, and NiO_2 NPs, have also shown similar OX-mimic activity [68][69][70][71], but their catalytic activity is relatively poor compared to natural enzymes [72]. Therefore, the need for cost-effective OX-mimic nanozymes with high catalytic activity and substrate specificity is of great interest. Recently, MOFs have gained considerable attention as OX-mimic nanozymes due to their small porous structure and capability of eliminating interference, thereby endowing them with high catalytic activity and substrate specificity.

2.2.1. Pristine MOF Nanozymes

Pristine MOFs, such as Ce-MOFs and Cu-MOFs, have been exploited as OX-mimics for MOF-based sensor development and therapeutic applications [73][74][75]. In one such report, Xiong et al. developed an OX-mimic MOF by using mixed valence Ce(III)/Ce(IV) as catalytic metal nodes, where the partial oxidation of Ce(III) in a mixed valent state caused the formation of Ce(III) and Ce(IV) redox couples with Ce(IV) performing OX-mimic activity [75]. Using a solvothermal process, Mao et al. synthesized an OX-mimic Cu(II)-MOF using 3-Amino-5-mercapto-1,2,4-triazole as an organic ligand [74]. The incorporation of the triazole unit Cu(II)-MOF showed excellent OX-mimic activity and initiated the TMB and ABTS oxidation in the absence of H_2O_2. In addition to this, Cu(II)-MOF showed strong antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [74]. While they do possess OX-mimic capabilities, these pristine MOFs exhibit poor catalytic activity and substrate specificity compared to natural oxidases. Therefore, synthesizing the MOF by stimulating the structural attributes of a natural enzyme would be a feasible strategy to address these limitations. In view of this, Li et al. synthesized a catechol oxidase-mimic MOF-NZ called MOF-818 by mimicking the active center (binuclear copper metal coordinated with six histidine molecules) of a catechol oxidase enzyme [73]. The developed MOF-818 exhibited excellent catechol oxidase-mimic activity and specifically oxidized 3,5-Di-tert-butylcatechol but not TMB and ABTS [73]. More such studies are important to increase the MOPF-NZ's catalytic performance and substrate affinity.

2.2.2. Modified MOF Nanozymes

Similar to modified POX-mimic MOF NZs, different modification strategies have been employed to increase the catalytic performance of MOF-NZs by altering the structural properties of MOF-NZs. Using MOFs as a superficial template, Cao et al. developed OX-mimic CeO_2 NPs by pyrolyzing Ce-MOF, wherein the Ce-metal ligands converted into ultra-small CeO_2 NPs (4 nm diameter), dispersing evenly on a porous carbonaceous framework [76]. Moreover, the pyrolysis created abundant oxygen vacancies in the CeO_2 nanozyme, facilitating easy oxygen exchange and superior OX-mimic activity. In another study, Chen et al. developed an excellent OX-mimicking MOF containing size-controllable Fe-N/C nanozymes by precipitating 2-Methylimidazole, $Fe(NO_3)_3{\cdot}9H_2O$, and $Zn(NO_3)_2{\cdot}6H_2O$ in methanol, followed by pyrolysis at 600–1000 °C to obtain a Fe-N/C catalyst [77]. The Fe-N/C catalyst serves as an electron acceptor and reduces subsequently adsorbed O_2 molecules to form reactive oxygen species (ROS), which resulted in the oxidation of the TMB substrate to produce a blue color. The Fe-N/C catalyst showed higher V_{max} and catalytic activity relative to Fe-N/C-CNT and free-Fe atoms; however, the catalyst showed lower substrate (TMB) affinity [77]. Interestingly, the catalytic activity varied significantly with pyrolysis temperature, pH, catalyst concentration, and catalyst particle size. Therefore, pyrolysis of MOFs could be a feasible strategy to enhance their catalytic performance.

Many previous studies have deployed metal/metal oxide NP encapsulation and heteroatom doping strategies to increase the OX-mimic catalytic performance and stability of OX-mimic MOF-NZs. In one such study, Zhang et al. developed a light-responsive OX-mimic AuNPs@NH_2-MIL-125(Ti) MOF-NZ by exploring the lower OX-mimic properties of Au NPs and a NH_2-MIL-125(Ti) MOF [78]. The developed MOF showed high substrate affinity (~16-fold lower K_m value) and reaction velocity (~1.4-fold higher V_{max}) for a TMB substrate compared to POX-mimic AuNPs@NH_2-MIL-125(Ti). Moreover, the

AuNPs on the NH_2-MIL-125(Ti) facilitated photo-generated charge transfer and separation, leading to higher photocatalytic activity. In another study, an OX-mimic Fe/Mn-MIL(53) MOF was developed by doping Mn ions [79]. The developed MOF showed higher catalytic activity due to increased electron transfer rate and $O_2^{\cdot -}$ generation from multiple redox couples (Fe^{2+}/Fe^{3+} and Mn^{2+}/Mn^{3+}). Moreover, the Fe/Mn-MIL-53 showed a 5-fold lower K_m value relative to Fe-MIL(53), exhibiting greater substrate affinity. Therefore, from the aforementioned studies, it is evident that an MOF modification with heteroatom doping and metal/metal oxide NPs could be a feasible strategy for attaining high OX-mimic activity; however, complex synthesis techniques and the requirement for toxic precursor molecules hinders their wide range of biomedical applications.

2.3. Superoxide Dismutase-Mimic

SOD is a crucial enzyme that carries out the simultaneous oxidation and reduction of unstable and toxic ROS, such as $^1O_2$, $O_2^{\cdot -}$ to H_2O_2, and is widely used for the treatment of ROS-induced health problems. However, the *in vivo* deployment of these enzymes has a few major challenges, including low storage stability, susceptibility to enzymatic aggregation and degradation, poor pharmacokinetics properties, and limited cellular uptake [80][81]. To overcome these challenges, immobilization or encapsulation into the porous matrix has been widely practiced. The encapsulation of SOD on porous MOFs using a biomimetic mineralization strategy increased the enzyme biocompatibility, stability, and activity and is considered a promising platform for *in vivo* biomedical treatment of ROS-mediated health problems. Using a similar approach, Guo et al. immobilized SOD using a Zr-MOF as a precursor. The SOD@Zr-MOF showed an excellent ROS scavenging property that significantly reduced mitochondrial damage and cell death and alleviated inflammation in the treated cells [80]. Bai et al. developed a SOD-encapsulated nanocomposite using zeolitic imidazole framework-zni (SOD@ZIF-zni) [82]. Compared to SOD, SOD@ZIF-zni showed high stability (temperature, pH, and storage), an *in vitro* anti-inflammatory effect, and therapeutic efficiency in treating inflammatory bowel disease [82]. Despite these merits, hybrid MOFs suffer from high synthesis costs and non-targeted action, which need to be addressed in the future. There are a few more reports which highlighted the SOD-mimic properties of MOFs and MOF composites, proving as an effective and excellent alternative to natural SOD for therapeutic applications [83][84][85]. A SOD-mimic cerium-based MOF using Ce(III) and Ce(IV) as an active site and 1,3,5-benzenetricarboxylic acid as an organic cross-linker was developed by Liu et al. for radioprotective applications against γ-radiation [84]. The Ce(IV)-MOF exhibited excellent SOD-mimic activity and demonstrated broad spectrum protection ability against γ-radiation by alleviating intracellular ROS and DNA damage without causing *in vivo* toxicity to exposed cells [84]. By mimicking the structural and functional attributes of natural SOD, Cu-tetrakis (4-carboxyphenyl) porphyrin MOF nanodots (Cu-TCPP-MOF NDs) were developed by coordinating Cu with N and O atoms [86]. The Cu-TCPP-MOF NDs showed excellent catalytic activity and efficiency as a ROS scavenger and catalyzed the enzymatic cascade reaction to convert H_2O_2 to H_2O. The Cu-TCPP-MOF NDs showed a dose-dependent cellular uptake, cytoprotective ability, low cytotoxicity, and excellent pharmacokinetics and renal clearance compared to natural SOD or SOD @MOF.

2.4. Catalase-Mimic

Like SOD, catalase (CAT) is another important antioxidant enzyme that complements SOD activity to convert unstable toxic $^1O_2$ or $O_2^{\cdot -}$ to H_2O and O_2. Natural CAT and CAT-mimic nanozymes can be used in biomedical applications for preventing ROS-mediated cell membrane damage, treating inflammatory disorders, tumor cell growth inhibition [87][88], and environmental remediation (biodegradation of organic contaminants) [89]. Despite their promising application potential in ROS-based therapeutic applications, natural CAT suffers due to poor thermal stability and easy inactivation under harsh acidic tumor environments [90]. To address these limitations, a few studies immobilized CAT enzymes into a MOF and achieved high stability, reusability, and catalytic activity under adverse conditions (pH and temperature) [91][92]. Recently, Sim et al. developed a CAT@MOF-888 nanocarrier system by the direct interfacial conjugation of a CAT molecule into a MOF-888 surface for the intracellular uptake and transfer of CAT. The MOF-888 enabled pH-responsive CAT detachment inside the cell and efficiently initiated ROS generation for photodynamic therapy of tumor cells [93]. Using the biomimetic mineralization encapsulation technique, Guo et al. immobilized CAT into ZIF-8 to achieve a highly stable and reusable CAT@ZIF8 MOF composite [94]. The resulting CAT@ZIF-8 exhibited exceptional catalytic activity, higher substrate (H_2O_2) affinity (K_m-value for CAT is 63.4 mM and CAT@ZIF-8 is 16.1 mM), and thermal (5–75 °C) and pH stability (5–9) compared to the natural CAT enzyme. Similarly, Liang et al. and Zhang et al. observed similar-to-higher catalytic performance and stability (temperature, organic solvents, and denaturing agents) of CAT-immobilized MOFs compared to natural CAT enzymes [95][96]. However, enzyme immobilization is a cumbersome process and is only successful when the enzyme is compatible with the size of the MOF cavity. Also, the surface attachment *via* covalent and non-covalent interaction might expose enzymes to proteolytic degradation and leaching [97]. To address this, some of the CAT-mimic cerium oxide (CeOx) NPs have been explored for therapeutic applications [98][99]. However, their efficiency *in vivo* application was compromised under harsh acidic conditions [100]. To protect cerium oxide from losing its catalytic

performance, Liu et al. embedded CeOx NP into the MIL-NH_2 (CeOx@MIL) *via* a surface modification to enhance its catalytic activity under a harsh hypoxic environment [101]. The outer MOF shell protected inner-core CeOx NPs; as a result, a 9-fold higher apoptotic efficiency was observed with the CeOx-MOF compared to pristine CeOx NPs [101]. Despite CAT-mimic nanozymes being promising agents in anti-inflammation and cancer therapy, studies exploring their development and application have remained limited, which calls for extensive efforts in this area.

2.5. Multi-Enzyme Assemblies

Apart from the aforementioned examples of MOFs mimicking a single-enzyme activity, certain MOFs can display multi-enzyme activities under different operating conditions or sometimes even under similar conditions. In other cases, MOFs with enzyme-like activity are combined with natural enzymes (enzyme@MOFs) to obtain multi-enzyme assemblies. The ability of MOFs, alone or with an enzyme, to display two or more enzyme activities has made them appropriate tools for cascade catalytic reactions and therapeutics. The structural versatility and tunable properties of MOFs have made MOFs suitable candidates for enzyme immobilization. In view of this, extensive efforts have been made to harness the potential of MOF-NZs in enzyme immobilization. In one such report, a GOx enzyme was encapsulated into the highly porous POX-mimic Au/MOFs(Fe, Mn)/CNTs composite [102], and in another, POX-mimic 2D-BTC MOFs were used for the encapsulation [103]. In both cases, authors could achieve ultrasensitive and selective glucose detection from the clinical specimens while maintaining the extended stability and reusability of the enzyme. In addition to immobilizing single enzymes in MOFs, efforts have also been made towards developing multi-enzyme cascade systems by immobilizing dual enzymes. In a recent report, Hou et al. developed a highly stable and biocompatible SOD@CAT@MOF hybrid complex by exploiting ZIF-8 as an exoskeleton scaffold and $MPEG_{2000}$-COOH for immobilizing SOD and CAT enzymes [81]. Interestingly, the developed MOF could not only demonstrate superior antioxidant properties for reducing H_2O_2 levels in simulated cell injury but also reduce ROS generation and enhance cell viability. It is worth noting that despite these merits, the encapsulated enzymes may exhibit reduced catalytic activity compared to their free counterparts and limited stability under ambient conditions, which calls for alternative approaches to develop multi-enzyme assemblies.

To this end, the incorporation of enzyme-mimicking metal or metal oxide NPs into the porous MOF construct has gained tremendous attention for achieving multi-enzyme-mimic assemblies that could potentially overcome the above-mentioned limitations. So far, various single and bimetal nanoparticles have been incorporated in POX-mimic MOFs to develop multi-enzyme mimic cascade complexes [104][105]. In a similar approach, Huang et al. combined the GOx-mimic Au NPs with POX-mimic Cu(II)-MOF nanosheets to develop a dual-enzyme mimic assembly and successfully exploited it for ultrasensitive glucose detection [104]. In another complex, intrinsic POX- and CAT-mimic Pt NPs were combined with a POX-mimic MOF(Fe) to develop dual-enzyme mimic MOFs [106]. Notably, the large surface area of MOFs allowed increased binding of Pt NPs and subsequently displayed more catalytic active sites. This, in turn, conferred the MOF complex with excellent catalytic activity and substrate affinity for H_2O_2 electrocatalysis than its pristine MOF counterparts.

Despite the merits of multi-enzyme mimic NP@MOF complexes, their requirement for tedious and challenging modification calls for facile alternatives to obtain complexes with desired properties. Prompted by this, Yang et al. fabricated a one-component multi-enzyme mimic Fe-PCN MOF by incorporating zirconium (Zr) ions as active metal nodes and Fe-porphyrin as an organic linker [107]. Interestingly, the developed MOF could exhibit superior intrinsic POX-, OX-, and phosphatase-like activities with Zr-O clusters providing active sites for both POX- and OX-mimics and Fe-centers for phosphatase-mimic activities. On account of this, the developed MOF could also demonstrate excellent sensitivity and substrate affinity for H_2O_2 detection under neutral conditions compared to other pristine MOFs and bimetallic systems. In another study, a mixed-valence Ce-MOF was designed by Luo et al. to mimic both POX and OX activities [108]. Notably, the developed MOF exhibited high substrate affinity (low K_m) and catalytic activity compared to HRP. Despite emerging advancements in the developing multi-enzyme mimic systems, most efforts have been limited to POX- and OX-mimic systems. In order to truly meet the versatility of natural enzymes, extensive efforts are required to explore the other enzyme-mimic activities. Given this, Yang et al. synthesized a SOD- and POX-mimic MOF complex by employing PEG modification and Cu-Pd alloy incorporation in the MIL-101 MOFs (Cu-Pd@MIL-101) [109]. Reportedly, the developed MOF complex could effectively demonstrate ROS-mediated tumor therapy by releasing toxic $^{\bullet}OH$ radicals in the tumor microenvironment. While systems like these present themselves as promising alternatives to natural SOD- and CAT-based therapies, challenges associated with their biocompatibility and effective target site delivery need to be addressed to realize their practical feasibility in biomedical therapy.

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