frontiers | Frontiers in Bioengineering and Biotechnology

TYPE Review
PUBLISHED 09 May 2024
DOI 10.3389/fbioe.2024.1363227

OPEN ACCESS

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RECEIVED 30 December 2023
ACCEPTED 12 April 2024
PUBLISHED 09 May 2024

CITATION
Chen M, Qin Y, Peng Y, Mai R, Teng H, Qi Z and Mo J (2024), Advancing stroke therapy: the potential of MOF-based nanozymes in biomedical applications.
Front. Bioeng. Biotechnol. 12:1363227.
doi: 10.3389/fbioe.2024.1363227

Advancing stroke therapy: the potential of MOF-based nanozymes in biomedical applications

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In this study, we explored the growing use of metal-organic framework (MOF)-based Nanozymes in biomedical research, with a specific emphasis on their applications in stroke therapy. We have discussed the complex nature of stroke pathophysiology, highlighting the crucial role of reactive oxygen species (ROS), and acknowledging the limitations of natural enzymes in addressing these challenges. We have also discussed the role of nanozymes, particularly those based on MOFs, their structural similarities to natural enzymes, and their potential to improve reactivity in various biomedical applications. The categorization of MOF nanozymes based on enzyme-mimicking activities is discussed, and their applications in stroke therapy are explored. We have reported the potential of MOF in treating stroke by regulating ROS levels, alleviation inflammation, and reducing neuron apoptosis. Additionally, we have addressed the challenges in developing efficient antioxidant nanozyme systems for stroke treatment. The review concludes with the promise of addressing these challenges and highlights the promising future of MOF nanozymes in diverse medical applications, particularly in the field of stroke treatment.

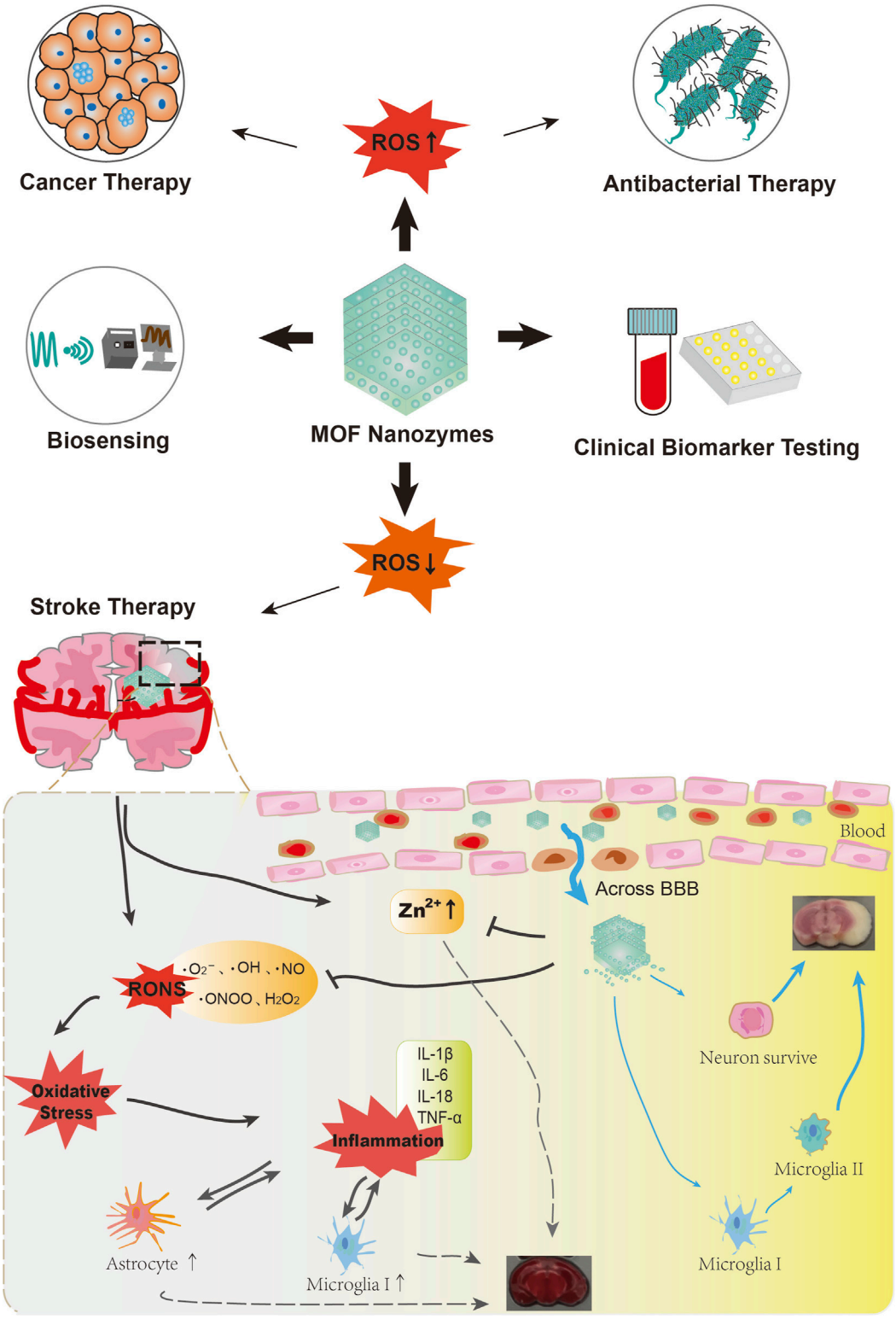
KEYWORDS

metal-organic frameworks, nanozymes, ischemic stroke treatment, reactive oxygen species, biomedical applications

1 Introduction

Stroke, a cerebrovascular disease characterized by sudden neurological deficits, presents a significant global public health challenge due to its high incidence, disability, and mortality rates. Occurring predominantly in developing countries, approximately 87% of all stroke cases are ischemic strokes (IS) (Saini et al., 2021; Feigin et al., 2022). The pathophysiology of IS complex, involving excitotoxicity, mitochondrial dysfunction, autophagy dysregulation, oxidative stress, and neuroinflammation (Stonesifer et al., 2017; Tuo et al., 2022). Inflammation is a major factor in primary and secondary brain damage post-IS (Boltze and Perez-Pinzon, 2022). An essential aspect of this pathophysiology is the abnormal increase in the levels of reactive oxygen species (ROS), which is directly associated with oxidative stress and inflammatory responses. Therefore, alleviating ROS is crucial in IS treatment.

ROS, which naturally results from oxygen metabolism, play crucial roles in cell signaling and maintaining oxidative balance *in vivo* (Qi et al., 2022). An imbalance in the equilibrium



GRAPHICAL ABSTRACT

between ROS production and elimination, whether due to antioxidant deficiency or ROS overproduction, can cause oxidative stress. This can contribute to several diseases such as aging, diabetes, cardiovascular, and inflammatory conditions, neurological disorders (including Parkinson's disease and Alzheimer's disease), and cancer (Chua et al., 2019; Talebi et al., 2022; Jomova et al., 2023).

Superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD) are natural enzymes known for their efficacy in scavenging reactive oxygen species (ROS). These enzymes,

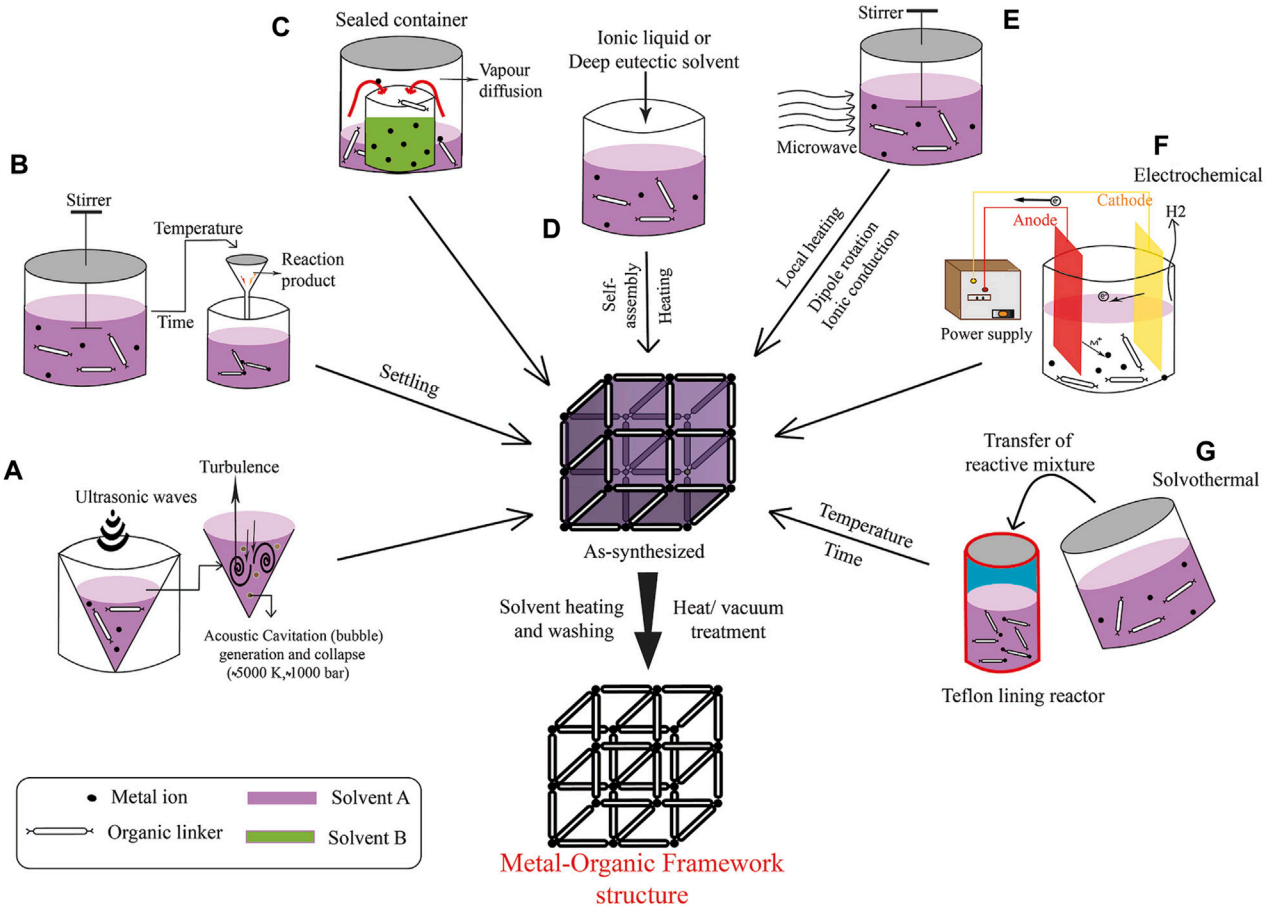


FIGURE 1
Overview of MOF Synthesis Techniques: **(A)** Sonochemical Approach, **(B)** Standard Solvothermal Method, **(C)** Vapor Diffusion Technique, **(D)** Iono-thermal Synthesis, **(E)** Microwave-Assisted Synthesis, **(F)** Electrochemical Assembly, and **(G)** Solvothermal Synthesis Process. (Referenced from (Sharanyakanth and Radhakrishnan, 2020)).

composed of proteins or RNAs, catalyze specific reactions, reducing activation energy and thereby regulating metabolic, energy conversion, and disease processes (Wang et al., 2023). However, their applicability is limited to mild conditions, and they pose challenges in terms of separation, purification, cost, stability, and large-scale production (Chang et al., 2020). Nevertheless, there has been a shift in research toward the development of enzyme mimics, including catalytic cyclodextrins, polymers, supramolecules, porphyrins, and dendrimer macromolecules, aiming to emulate the functions of natural enzymes (Wulff, 2002; Wei and Wang, 2013).

In recent decades, the pursuit of mimicking the catalytic functions of natural enzymes has led to the emergence of artificial enzymes, which are designed to replicate the catalytic activities of their natural counterparts under laboratory conditions (Chen and Gridnev, 2020). Historically, artificial enzymes, including catalytic antibodies, peptide-based catalysts, and organic molecule-based catalysts, have offered promising avenues for research and applications (Zhang et al., 2019). However, challenges related to their stability, cost, and efficiency under physiological conditions have propelled the development of nanozymes.

Nanozymes, leveraging the advancements in nanotechnology, are engineered nanomaterials that exhibit enzyme-like activities (Singh, 2019; Villalba-Rodríguez et al., 2023). Offering advantages in terms of stability, affordability, and ease of preparation, nanozymes are positioned as ideal substitutes for natural enzymes. Over the last decade, nanozymes have been used in various fields, including biomedicine, food, and the environment (Ma et al., 2020; Shang et al., 2020; Curulli, 2021; Jiang et al., 2021; Khan et al., 2021; Ren et al., 2022; Wang et al., 2022). While most nanozymes exhibit oxidoreductase-like activities, some mimic SOD or CAT by scavenging ROS, whereas others function similarly to POD or oxidase (ODX) by generating ROS (Zhao et al., 2019; Liu et al., 2020). Despite the increasing variety of nanomaterials with enzyme-like activities, challenges persist in developing antioxidant nanozyme systems, such as achieving satisfactory catalytic activity, enabling multiple catalytic reactions, and ensuring good immunogenicity. Thus, antioxidant nanozymes with high activity, specificity, biosafety, and well-defined structures should be developed for therapeutic applications.

Among various nanozymes, Metal-Organic Frameworks (MOFs) based nanozymes stand out due to their unique structural features and tunable catalytic properties, offering new

TABLE 1 The main classification of MOF nanozymes.

Mimic enzyme	Classification	Application	Reaction principle	References
OXD	Ce-MOF	Detection of biothiols in serum samples and of dopamine in sweat samples	Colorimetric detection, colorimetric sensing	Xia et al. (2022), Xiong et al. (2015)
	Co-MOF	Detection of ultra-trace triazine endocrine disruptors and differentiation of aminophenol isomers	Colorimetric detection	Du et al. (2023), Ren et al. (2023)
	Cu-MOF	Screening for alpha-glucosidase inhibitors	Colorimetric sensing	Zhong et al. (2020)
	MnO-MOF	Cholesterol level determination	Catalytic oxidation	Xu et al. (2021)
	Co/2Fe-MOF	Sialic acid test	Oxidation reaction	Kıyıkçı et al. (2023)
POD	Fe-MOF	Alzheimer's treatment	Bio-optical sensing	Miao et al. (2022)
	Cu-MOF	Optical biosensor detects C-reactive protein, anti-cancer	Colorimetric (fluorescence) detection, Fenton-like reaction	Hao et al. (2021), Ali and Omer (2022)
	Ni-MOF	Label-free fluorescence detection of hydrogen peroxide and glucose	Non-fluorescent labelling of hydrogen ions	Guo et al. (2022)
	Zr-MOF	Phosphorylated protein differentiation	Colorimetric sensing	Wang et al. (2020)
	Tb-MOF	Detection and degradation of estrogenic endocrine disruptors	Oxidative degradation	Wang and Chen (2020)
	Ni/Fe-MOF	Detection of hydrogen peroxide and glutathione	Colorimetric detection	Li et al. (2021)
	Au/Fe-MOF	Determination of prostate-specific antigen	Fenton-like reaction	Feng et al. (2020)
	Fe/Eu-MOF	Dual-mode alkaline phosphatase sensor	Accelerated fluorescent quenching	Shi et al. (2021)
	MOF-818	Detection of H_2O_2 and H_2S levels released from living cells	Colorimetric and electrochemical dual-mode sensor	Yu et al. (2023)
Glutathione Peroxidase (GPx)	MIL-47(V)-NH2	Alleviate the inflammatory response effectively for both ear injury and colitis	Maintaining the reactive oxygen metabolic balance and protecting against injury by removing the excess H_2O_2	Wu et al. (2021)
CAT	Ce-MOF	Protection against iron overload damage in thalassemia and cancer	Elimination of ROS and iron overload, catalytic ATP depletion	Duan et al. (2023), Zhe et al. (2023)
	Mn-MOF	Enhancement of anti-tumor immunity and improvement of the immunosuppressive microenvironment; inflammatory bowel disease therapy	Promotion of ROS and iron death formation, thereby assisting in cancer inhibition and ROS-removal via sonodynamic therapy	Xu et al. (2021), Chen et al. (2022)
	Fe-MOF	Photodynamic therapy against tumors	Promoting ROS formation and assisting in photodynamic therapy for cancer inhibition	Liang et al. (2023)
	PCN-224-Pt	Cancer photodynamic therapy	Induction of H_2O_2 decomposition in tumors to generate $^1O_2$, leveraging the cytotoxic potential of the produced $^1O_2$ for cancer cell eradication	Zhang et al. (2018)
	Cu-MOF	Monitoring and management of bacterial-infected wounds	Decomposition of hydrogen peroxide	Mo et al. (2023)
SOD	Cu-MOF	Modelling superoxide anion sensing and removal of superoxide anion	Scavenging the oxygen catalytic activity	Guan et al. (2023)
	Ce-MOF	Protecting against iron overload damage in thalassemia	ROS-removal and iron-overload elimination	Duan et al. (2023)
Hydrolase	Ce-MOF	Glycopeptide analysis, prothrombin assay	Catalyzing self-cascading reactions	Pu et al. (2020), Yu et al. (2018)
Glucose oxidase (GOD)	TGZ@eM	Cancer-starvation therapy for colon cancer	Delivering GOD to tumor cells and degrading glucose to disrupt the tumor's nutrient supply	Zhang et al. (2018)

(Continued on following page)

TABLE 1 (*Continued*) The main classification of MOF nanozymes.

Mimic enzyme	Classification	Application	Reaction principle	References
Multi-enzyme system	$Mn_3[Co(CN)_6]_2$ MOF	Antitumor	Exert POD-like and OXD-like activities, catalyze the generation of O_2 from endogenous H_2O_2, and facilitate the conversion of O_2 into cytotoxic ROS	Wang et al. (2020)
	PyroFPSH	Photodynamic therapy for cancer	Overcome apoptosis resistance, reduce endogenous glutathione levels, and continuously generate ROS, due to remarkable multienzyme-like activities (GPx/CAT mimicry)	Lv et al. (2023)
	Fe-MIL-88NH_2	Biofluid management and bacterial infection treatment	Excellent POD and OXD mimicry activities (the generation of •OH and $•O_2^-$ radicals)	Li et al. (2021)
	GATC	Monitoring and Management of Bacteria-Infected Wounds	With triple-enzyme activities, including POD, CAT and GPx mimicry, producing more •OH to kill bacteria, decomposing H2O2 into O2 to alleviate hypoxia and avoiding the loss of •OH for bacterial death more easily	Mo et al. (2023)
	Fe (III)-BTC-type MOF	Cascade colorimetric determination of glucose	With POD-like and GOD-like activities, during GOD's enzymatic oxidation, glucose consumption, and H_2O_2 production, leading to the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) by POD mimic, thereby forming a blue-green product	Zhao et al. (2019)

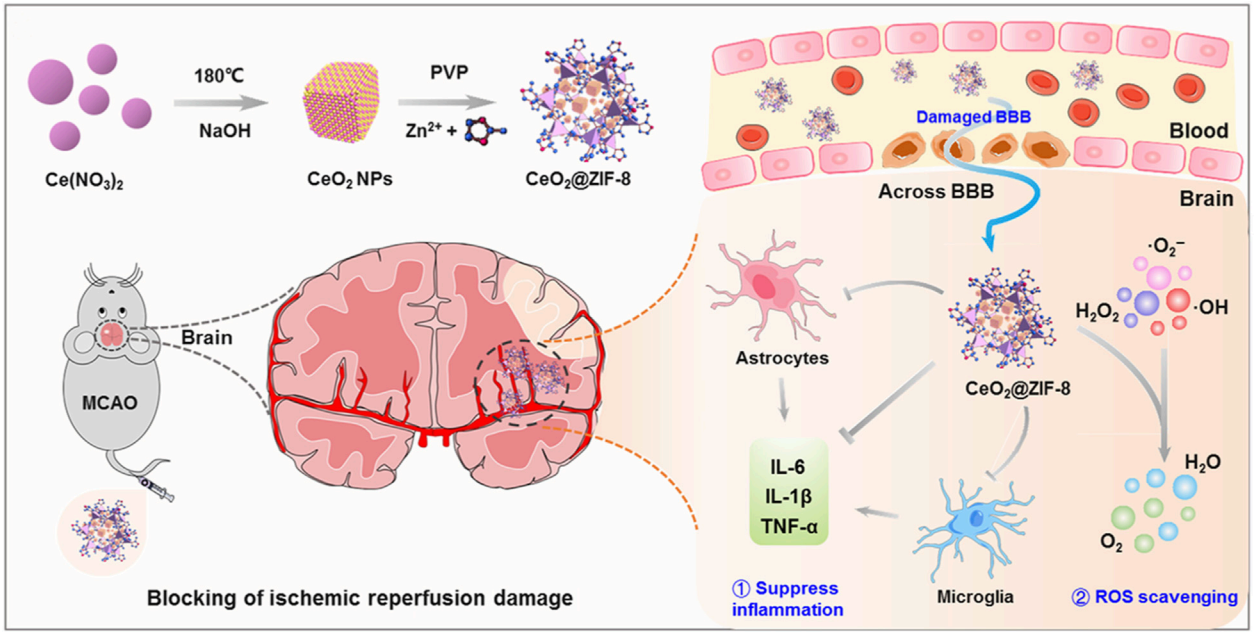


FIGURE 2
Schematic illustration for *in situ* synthetic approach of CeO2@ZIF-8 nanotherapeutics and its neuroprotective application mechanisms against reperfusion-induced injury in ischemic stroke. ref to (He et al., 2020).

horizons in biomedical applications (Christodoulou et al., 2023). MOFs are ordered porous crystalline materials formed through the self-assembly of metal ions/clusters and multidentate ligands. They exhibit structural similarities to natural enzymes (Li et al., 2015; Abednatanzi et al., 2019). Their composition includes valence metals (serving as catalytic sites), organic ligands (acting as framework modulators), and pore structures (allowing mass transfer in catalytic reactions) (Lee and Telfer, 2023). MOFs have garnered increasing attention due to their high specific surface area, porosity, adjustable cavity structures, and biosafety. Their catalytic abilities are attributed to redox-active metal ions (such as Fe, Cu, Co, Ni, and Ce) and specialized organic ligands, which act as electronic mediators and mimic natural enzyme catalysis (Konavarapu et al., 2019; Wu et al., 2020; Li et al., 2021; Rojas-Buzo et al., 2021; Bohan et al., 2024). In

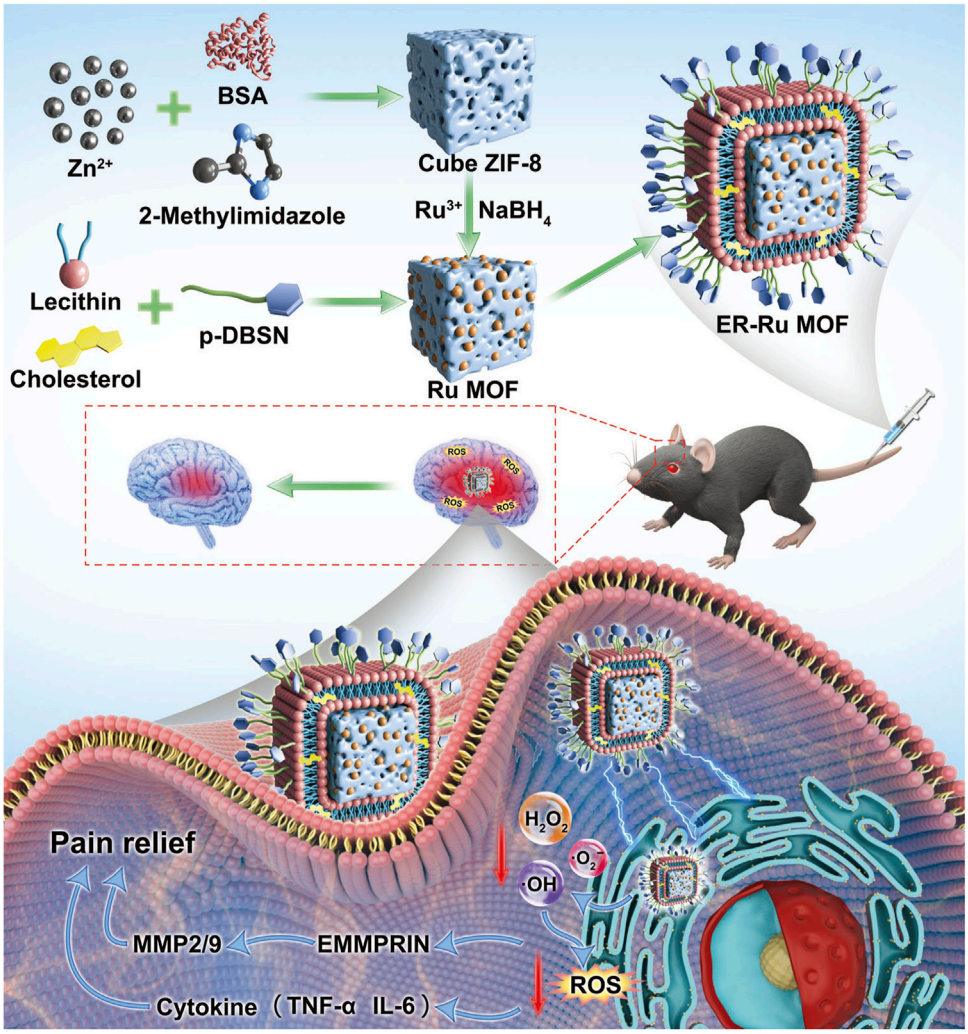


FIGURE 3
Schematic illustration of ER-Liposome encapsulated MOF tailored for therapeutic mechanisms on central post-stroke pain focused on oxidative stress regulation. (Referenced from (Bai et al., 2023)).

this review, we have classified MOF-based nanozymes and provided a summary of their application in the medical field, with a specific focus on applications in stroke treatment.

2 Synthesis of metal-organic frameworks

The synthesis of MOFs, as shown in Figure 1, can be achieved via various methods, each customized to attain specific structural and functional properties. One of the primary methods is solvothermal synthesis, wherein a metal salt is mixed with a multitopic organic linker in a high-boiling-point solvent such as N, N′–dimethylformamide (DMF), Diethyl formamide (DEF), or dimethyl sulfoxide, in a screw-top vial (Shi et al., 2004; Mohanty et al., 2010). The mixture is then heated, typically for 1–48 h. After completion of the reaction, the mixture is allowed to cool at room temperature. Subsequently, to remove impurities, the product is washed several times in succession with a deionized solution (such as water). The pure MOFs are obtained following centrifugation, washing with deionized solution, and vacuum drying.

Key parameters that can be changed during the process include reaction temperature, time, solvent, reagent concentration, pH, and the nature of the precursors. These factors can affect the topology, crystal size, and phase purity of the resulting MOF. Single crystals are readily available using this method, and single crystal x-ray diffraction can be used for structural characterization. Therefore, this method is highly selective for synthesizing MOF. This method can be used for the synthesis of porphyrin MOFs (PMOFs) and meso-tetra (4-carboxyphenyl) porphyrin (TCPP) MOF (Yan et al., 2023; Yu et al., 2024).

In instances where metal–ligand bonds exhibit exceptional strength, modulators are used to prevent the rapid precipitation of amorphous material. Modulators, such as benzoic acid, acetic acid, or hydrochloric acid, establish dynamic bonds with the metal precursor, competing with the linkers for metal coordination sites (Sugamata et al., 2020; Mao et al., 2022). They play a crucial role in the synthesis of Zr-MOFs, which contain robust Zr (IV)–O bonds.

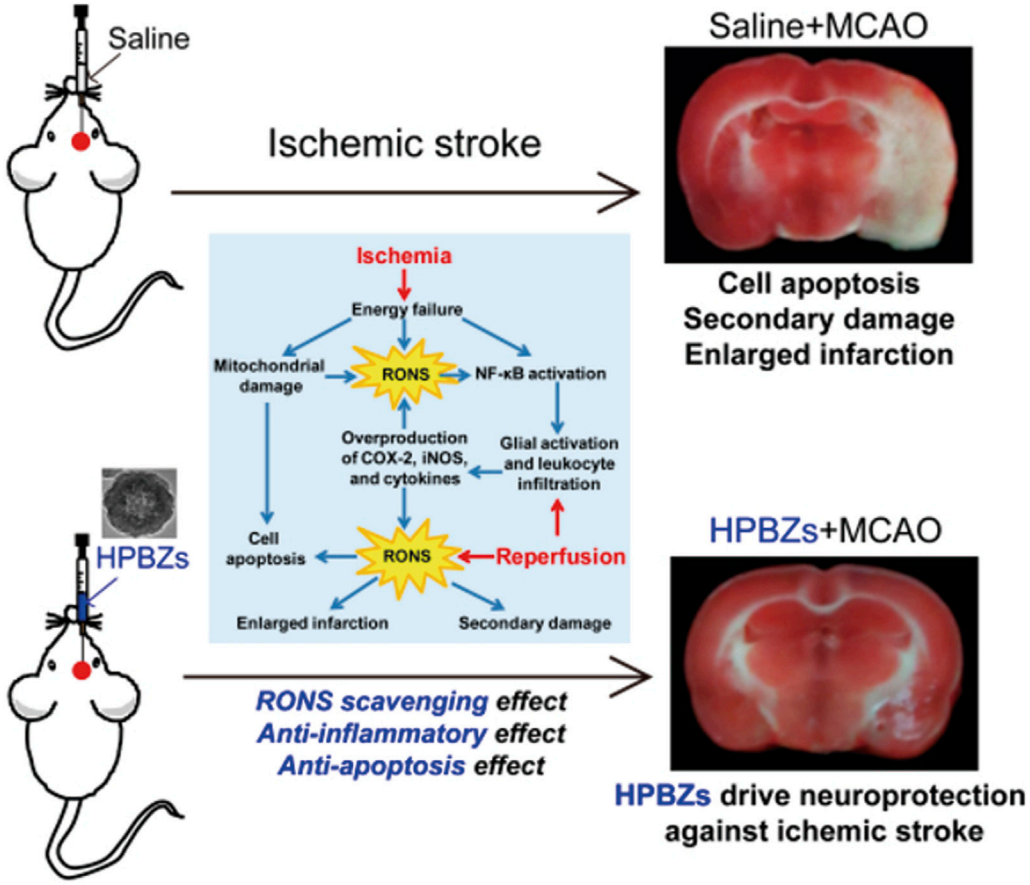


FIGURE 4
Schematic diagram of HPBZs driving neuroprotection against ischemia/reperfusion injury. (Reference (Zhang et al., 2019)).

The selection of the modulator, its chemical composition, and concentration can significantly affect the defects, crystal size, habit, and topology of the MOF.

An alternative approach to traditional MOF synthesis involves the preformation of metal nodes or secondary building units (SBUs) (Zhou et al., 2018; Bour et al., 2020). This method includes the initial synthesis and isolation of metal cluster nodes, which are mixed with a tetratopic porphyrin-based linker and an acid modulator in DMF. Moreover, the preformation of metal clusters can optimize the phase purity and surface area of the MOF.

Other strategies for MOF synthesis include electrochemical, mechanochemical, sonochemical methods, and microwave-assisted synthesis (Hwang et al., 2005; Ni and Masel, 2006; James et al., 2012; Campagnol et al., 2014; Phang et al., 2014; Sharanyakanth and Radhakrishnan, 2020). To create MOF thin films, methods such as layer-by-layer deposition, liquid phase epitaxial growth, or seeded growth on a coated substrate are used. Moreover, post-synthetic methods, such as post-synthetic modification (PSM), solvent-assisted linker exchange (SALE), and transmetalation, enable the replacement of organic linkers or metal nodes in an existing MOF to create a new framework with the same topology.

Although the same reaction mixture (such as metal source, organic ligand, and solvent) is used in the formation of MOFs, the structures can differ due to differences in reaction time, particle size, yield, and morphology. Therefore, synthetic MOFs that are synthesized by different methods can vary. Different synthesis methods have their own advantages and disadvantages. Additionally, several MOF materials can be produced by various techniques that mix a large amount of available components and through variable process parameters.

3 MOF-based enzyme simulation system

MOFs, characterized by their unique porous structures and versatile functionalities, have emerged as promising tools for simulating enzymes. The majority of reported MOF nanozymes exhibit activities similar to oxidoreductases and resemble natural enzymes. For example, nanozymes mimicking the activities of SOD and CAT can scavenge ROS, protecting against oxidative stress. Conversely, those emulating POD and OXD can generate ROS, targeting harmful entities such as tumor cells and bacteria. This dual ability to both scavenges and generate ROS broadens the applicability of MOFs in biomedicine. Table 1 below classifies nanozymes based on their enzymatic activities and highlights their applications in the field of biomedicine.

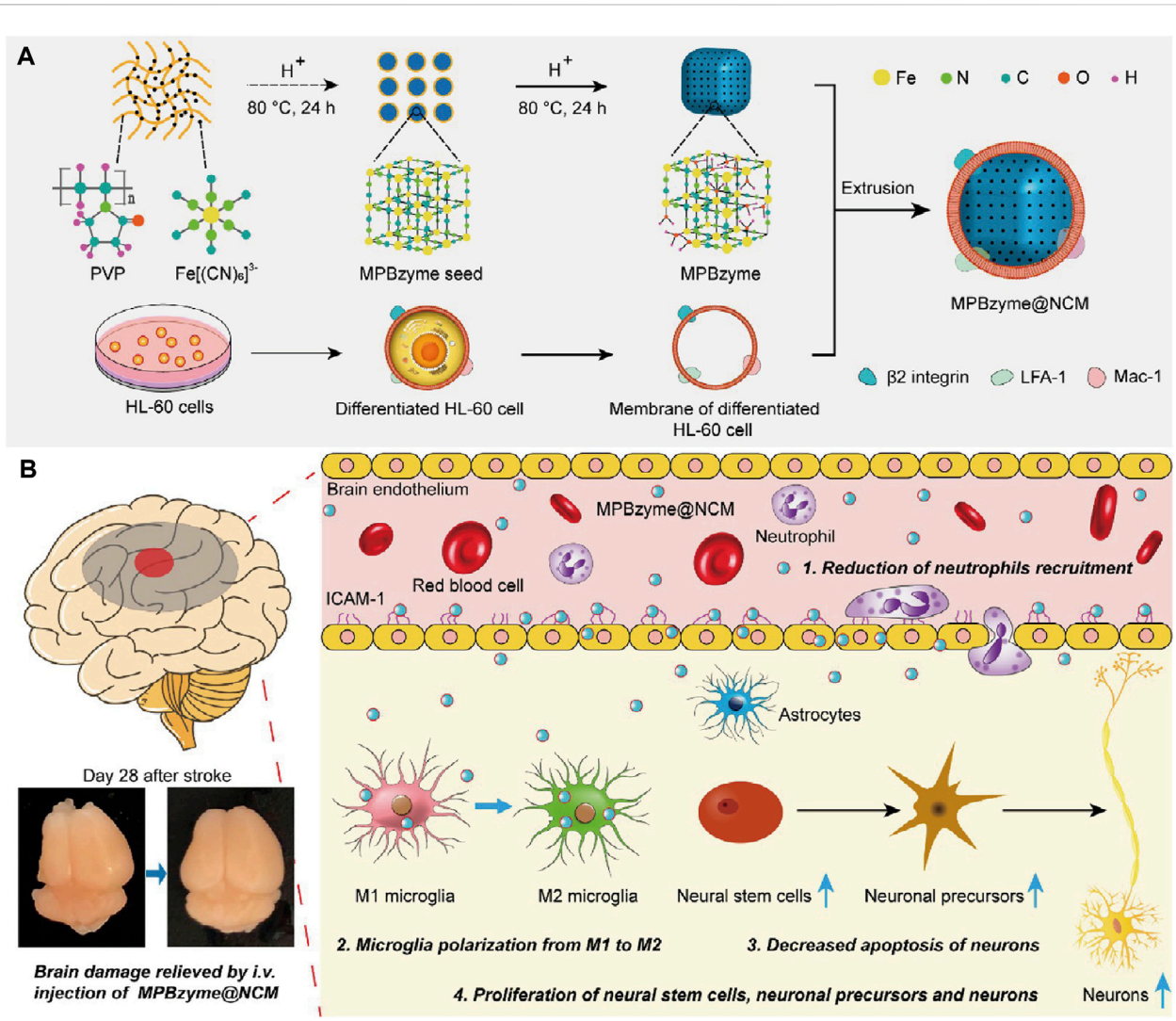


FIGURE 5
Schematic Representation of Neutrophil-Like Cell-Membrane (NCM)-Coated Nanozyme (MPBzyme@NCM) in the Treatment of Ischemic Stroke. **(A)** Scheme of the MPBzyme@NCM synthesis process. **(B)** Illustration of MPBzyme@NCM therapy for ischemic damage and long-term neurological functional recovery. Coating of NCM efficiently enhanced the penetration of nanozyme across brain microvascular endothelial cells. The MPBzyme@NCM elicited long-term therapeutic efficacy after stroke by reducing neutrophil recruitment, driving microglia polarization from M1 to M2, decreasing apoptosis of neurons, andincreasing the proliferation of neural stem cells, neuronal precursors, and neurons. (Referenced from (L. Feng et al., 2021)).

4 Catalytic mechanism of MOF-Based nanozymes

MOFs offer a unique blend of metal ion reactivity, organic linker functionality, and structural porosity that mimics the efficiency and specificity of natural enzymes (Islamoglu et al., 2017). The catalytic activity of MOF-based nanozymes is attributed to their hybrid composition of metal nodes acting as catalytic centers and organic linkers that enhance substrate specificity and catalytic efficiency (Zhang et al., 2019). These nanozymes are capable of performing electron transfer reactions akin to natural oxidoreductase enzymes, such as catalases and superoxide dismutases, demonstrating their potential in scavenging reactive oxygen species and offering new pathways for biomedical applications (Niu et al., 2020). Recent advancements highlight the potential of MOFs to incorporate multienzyme systems, achieving synergistic activities that could address oxidative stress-related disorders effectively (Bai et al., 2024). This confluence of features underscores MOFs' versatility in biomedical fields, paving the way for the development of advanced therapeutic agents with tailored catalytic properties.

5 The application of nano-enzymes using MOF for stroke treatment

Stroke is a severe acute cerebrovascular disease, which is broadly classified into hemorrhagic stroke and IS. IS characterized by cerebral infarction or arterial blockage, causing symptoms such as hemiplegia or impaired consciousness. It is the leading cause of morbidity, recurrence,

TABLE 2 The advantages of MOF nanozymes in stroke treatment and action mechanisms.

Classification	Advantages	Action mechanism	References
CeO2@ZIF-8	Improves drug stability, biocompatibility, and prolongs its circulation time within the bloodstream, thereby enhancing the catalytic and antioxidative activities	Encapsulates CeO_2 NPs with stable, biocompatible shells, such as ZIF-8, to prolong the blood circulation time of CeO_2, reduce the clearance rate, improve the penetration across the BBB, and enhances its accumulation in the brain tissues, ZIF-8, mimics POD, disintegrates or absorbs H_2O_2, thereby exerting antioxidant activity	He et al. (2020)
ZIF-67/ Cu0.76Co2.24O4 NSs	Induces the formation of cascade-reaction systems with a high overall activity	Effectively clears ROS and abrogated oxidative stress with POD-like, SOD-like, GPx-like, and laccase-like activities	Liu et al. (2020)
	Enables near real-time monitoring of DOPAC, a brain-damage biomarker, in rat brain microdialysate	Catalyzes 3,4-dihydroxyphenylacetic acid (DOPAC) into anthraquinones	
ZIF-L-Co	Improves the selectivity of the online electrochemical system for UA detection in rat brain microdialysate	Enhances catalytic activities of ascorbate oxidase and lyase	Qu et al. (2019)
ER-Ru MOF	Facilitates better targeting and thus better drug concentration at the site of injury	Nanozyme encapsulated in an endoplasmic reticulum-targeted liposome ER-Ru MOF to thalamic hemorrhage pain, exhibiting SOD/CAT cascade catalytic activities to scavenge mitochondrial ROS and RNS	Bai et al. (2023)
(PB) MOF	Presents excellent biosafety	PB nanozyme with multienzyme activity (SOD-like and CAT-like) efficiently scavenge ROS, reduce toxicity of •OH and inhibit macrophage activation, neuronal cell apoptosis	Liu et al. (2023)
HPBZs	Increases brain tolerance of ischemic injury with minimal side effects	HPBZs, with their hollow structure and multienzyme activity, robustly scavenge RONS, converting them into harmless molecules and mitigating oxidative stress, apoptosis, and inflammation	Zhang et al. (2019)
2MI-P@MSN	Regulates intracellular excess free Zn^{2+} with excellent biocompatibility and non-cytotoxicity	2MI-P@MSN displays a "turn-on" fluorescence signal for Zn^{2+}, chelate intracellular Zn^{2+}	Chai et al. (2021)
		Besides, ZIF-8 with POD-like activity, effectually scavenge ROS	
Fe2NC@Se	Possesses multi-enzyme cascade antioxidant activity	Encapsulates a double iron atom nano-enzyme (Fe_2NC) in a selenium-containing MOF (Se-MOF) shell layer, with SOD, CAT, and GPx-like activities, effectively eliminate intracellular ROS and inhibit the ASK1/JNK apoptosis pathway, thereby reducing oxidative damage and neuronal apoptosis post-CIRI	Ruizhen Tian et al. (2022)
INAzymes	Facilitates glucose detection and monitoring of striatal glucose changes after cerebral ischemia/reperfusion	Integrate nano-enzymes by embedding hemin and GOD in ZIF-8 nanostructures; the product of the first reaction can be used immediately as a substrate for the second reaction, which overcomes the problems of diffusion-limited kinetics and product instability and improves the catalytic activity and stability	Cheng et al. (2016)
MPBzyme@NCM	Enhances the BBB penetration and delivery of MOF Nanozymes to the ischemic brain	Realizes noninvasive active-targeting therapy for ischemic stroke using neutrophil-like cell-membrane-coated mesoporous MPBzyme@NCM, based on innate connection between inflamed brain microvascular endothelial cells and neutrophils after stroke	Feng et al. (2021)
		PB nanozyme with SOD/CAT-like activities efficiently scavenge ROS and decrease apoptosis of neurons	

death, and disability (Kamtchum-Tatuene and Jickling, 2019; Kapoor et al., 2019). The current FDA-approved treatment for IS includes a tissue plasminogen activator, which can effectively dissolve thrombi within a narrow therapeutic window of 4.5 h. However, only a few patients can benefit from this. Another treatment option includes interventional therapy, which is limited by stringent technical and patient condition requirements and can pose risks such as cerebral hemorrhage (Kim, 2019).

5.1 Scavenging ROS and evading oxidative stress

The 'sensitivity of the brain toward ischemia and hypoxia arises from its dependence on oxygen and glucose supplies, lacking significant energy reserves. Cerebral ischemia can cause hypoxia, rapid energy depletion, and subsequent nerve cell depolarization and excitatory neurotransmitter (glutamate) release (Dirnagl et al., 1999). This can trigger cellular excitotoxicity, resulting in cell

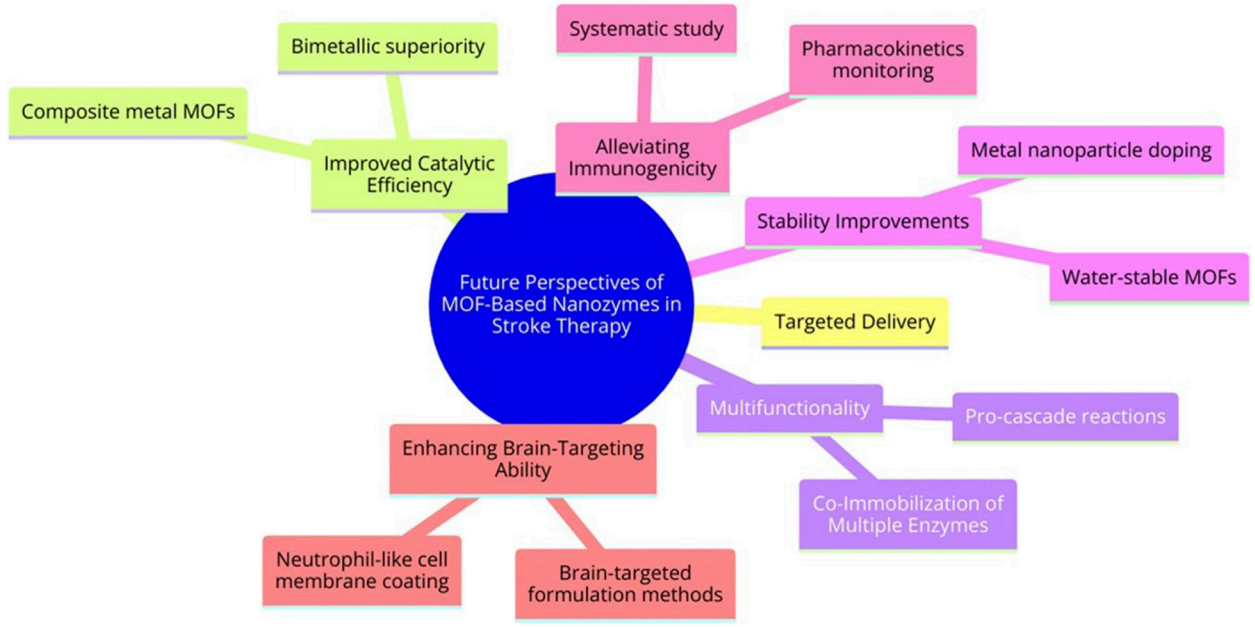


FIGURE 6
Future perspectives of MOF-Based nanozymes in stroke therapy.

swelling. Intracellular Ca^{2+} overload activates many enzyme systems, causing membrane disruption and the production of substantial amounts of ROS and reactive nitrogen species (RNS), which can activate apoptosis, necrosis, and autophagy, finally determining infarct size (Li et al., 2023). Oxidative stress is a result of ROS/free radicals and antioxidant system imbalance, which can be countered by natural antioxidants. Therefore, drugs with potent ROS-scavenging abilities should be developed (Betteridge, 2000; Li et al., 2018; Feigin et al., 2022).

Many nano-antioxidants, including ferric, manganese, magnetite, and cerium dioxide (CeO_2) nanoparticles, have been constructed for stroke treatment (Kwon et al., 2018; Tao et al., 2019; Liu et al., 2021; Ma et al., 2023; Salatin et al., 2023; Wang et al., 2023). CeO_2 NPs are particularly advantageous for their high antioxidant activity and recyclable ROS scavenging capability due to the fluorite lattice structure and the electron transfer between Ce^{3+} and Ce^{4+} (Bao et al., 2018; Li et al., 2022). 'A study by Kim revealed CeO_2 NPs as effective free radical scavengers, which can prevent neuron damage from oxidative stress during IS (Kim et al., 2012). Nevertheless, challenges such as short vascular circulation time, interparticle aggregation, and direct catalytic reaction on active sites hinder their clinical application. Encapsulating CeO_2 NPs with stable, biocompatible shells, such as zeolite imidazoline framework-8 (ZIF8), improves their properties and applicability (Zhu et al., 2021). As shown in Figure 2, He et al. innovatively synthesized ZIF-8-capped CeO_2 NPs (CeO_2@ZIF-8), which have improved catalytic and antioxidative activities. ZIF-8 mimics POD and can disintegrate or absorb H_2O_2, thereby exerting antioxidant activity. The CeO_2 core containing the ZIF-8 layer is ideal for biological applications due to its controlled size, shape, and surface charge. The synergy between ZIF-8 decomposition and CeO_2 release improves stroke treatment efficacy. Furthermore, CeO_2@ZIF-8 NPs can effectively scavenge ROS (•OH, $•O_2^-$, and H_2O_2) and protect neuronal cells in MCAO model mice (He et al., 2020).

5.2 Integrated cascade nanozymes for stroke treatment

The development of cascade Nanozymes mimicking anti-ROS therapy is an effective strategy. 'Liu et al. established an integrated cascade nanozyme (Pt@PCN222-Mn), combining Mn-based MOF compounds (mimicking SOD) that can convert oxygen radicals into H_2O_2 and platinum nanoparticles that can (mimicking CAT) disproportionate H_2O_2 into water and oxygen. This cascade nanozyme exhibits excellent ROS scavenging ability in inflammatory bowel disease models (Liu et al., 2020).

Based on this aforementioned concept, Liu (Liu et al., 2020) designed an online electrochemical detection system using a rat cerebral ischemia model. This system used ZIF-67/$Cu_{0.76}Co_{2.24}O_4$ nanospheres (ZIF-67/$Cu_{0.76}Co_{2.24}O_4$ NSs) synthesized via alcohol heating with $Cu(NO_3)_2$. These nanospheres, possessing POD-like, SOD-like, GOD-like, and laccase-like activities, can effectively clear ROS and evade oxidative stress. They can catalyze 3,4-dihydroxyphenylacetic acid (DOPAC) into anthraquinones, allowing near real-time monitoring of DOPAC, a brain damage biomarker, in rat brain microdialysate.

In a previous study, Co-containing ZIF with cysteine-induced structural defects (ZIF-L-Co) was introduced, exhibiting improved catalytic activities of ascorbate oxidase and lyase. This helped in monitoring uric acid (UA) levels in the brain. The increased selectivity of the online electrochemical system for UA detection in rat brain microdialysate highlights the potential of this system for cerebral ischemia treatment and therapeutic effect assessment (Qu et al., 2019).

The use of MOF nano-enzymes in stroke treatment marks a promising shift in neuroprotective therapeutics, particularly in addressing IS. These innovative nano-enzymes, such as exhibited Pt@PCN222-Mn and ZIF-67/$Cu_{0.76}Co_{2.24}O_4$ NSs, have remarkable efficacy in scavenging ROS and alleviating oxidative stress, pivotal factors in cerebral ischemia. Their ability to closely emulate natural antioxidant enzymes, along with enhanced stability and biocompatibility, highlights their potential to revolutionize stroke treatment. This advancement not only improves the effectiveness of presently used therapies but also paves the way for real-time monitoring and targeted intervention, allowing improved patient outcomes in cerebrovascular health.

5.3 Regulating reactive oxygen and nitrogen species and alleviating inflammatory response and apoptosis in stroke treatment

The overproduction of reactive oxygen and nitrogen species (RONS) in IS, such as •NO and •ONOO, can exacerbate brain damage. Excessive •NO can interact with $•O_2^-$, forming •ONOO and •OH and causing toxic effects (Ebrahimkhani et al., 2014; Yang et al., 2022). The inflammatory cascade is promptly triggered after vascular occlusion, which involves injury-associated molecular patterns and cytokines that can activate pattern recognition receptors (PRRs) on microglia and astrocytes (Gross et al., 2011). PRRs can detect injury-associated molecular patterns via toll-like receptors and inflammasomes (X. Y. Xiong et al., 2016).

Microglia activation, occurring within hours of an ischemic event, can cause the release of cytokines such as IL-1β, IL-6, IL-18, TNF-α, and NO, further perpetuating the inflammatory response (Jayaraj et al., 2019). Activated astrocytes can contribute to this process via the production of pro-inflammatory and anti-inflammatory cytokines (Ronaldson and Davis, 2012). Excessive accumulation of RONS can deactivate endogenous antioxidant enzymes, causing oxidative damage, especially in the ischemic penumbra (Schaller and Graf, 2004).

To address these limitations, Bai et al. (2023) constructed a ruthenium (Ru) MOF nanozyme encapsulated in an endoplasmic reticulum-targeted liposome (ER-Ru MOF), exhibiting SOD/CAT cascade catalytic activities, which can scavenge mitochondrial ROS and RNS. In a central post-stroke pain mouse model, ER-Ru MOF can significantly decrease the levels of pro-inflammatory cytokines and exert neuroprotective effects (Figure 3).

Prussian blue (PB) MOF Nanozymes are FDA-approved and known for their biosafety. They have also shown promising advantages in stroke treatment. PB Nanozymes can efficiently scavenge ROS due to their multiple enzyme-like activities (Estelrich and Busquets, 2021). Unlike iron-based nanoparticles, PB nanoparticles can inhibit •OH production, reducing toxicity (Zhao et al., 2018). Liu (J. Liu et al., 2023) demonstrated that PBzyme can inhibit macrophage activation, and neuronal cell apoptosis, and increase neurological recovery post-stroke by scavenging excess ROS.

Zhang et al. (2019) optimized the synthesis of hollow Prussian blue nanozymes (HPBZs) with multi-enzyme activity for RONS scavenging in a rat model of IS (Figure 4). HPBZs have a hollow structure and excellent redox ability, which can robustly scavenge RONS and convert them into harmless molecules. This can help in alleviating oxidative stress, apoptosis, and inflammation.

MOF nano-enzymes have emerged as potent therapeutic agents for stroke treatment, with a focus on scavenging ROS and RONS, as well as modulating inflammatory responses. Studies have reported the effectiveness of many MOF nano-enzymes in alleviating oxidative stress and inflammatory cytokines, protecting neuronal cells, and facilitating recovery in stroke models. The development of nano-enzymes, such as ER-Ru MOF and HPBZs, showcases the potential of MOFs in neuroprotection, emphasizing their role in advancing stroke therapy. This research lays the foundation for future innovations in the treatment of cerebral ischemia and other RONS-related diseases.

5.4 Regulating intracellular excess free Zn^{2+} and alleviating neuron apoptosis

Under normal physiological conditions, Zn^{2+} are protein-bound and play important roles in different biochemical functions, keeping free Zn^{2+} levels low (Frederickson et al., 2005). Nevertheless, during IS and reperfusion, an excess of protein-bound Zn^{2+} is released (Medvedeva et al., 2017). This increase in free Zn^{2+} can activate multiple pathways, such as glyceraldehyde-phosphate dehydrogenase (GAPDH) and glutathione reductase, thus triggering the transient receptor potential melatonin-associated 2 (TRPM2) pathway and resulting in neuronal cell injury and apoptosis (Mortadza et al., 2017). Addressing Zn^{2+} and ROS-associated cerebral ischemia-reperfusion injury (CIRI) is challenging because most studies focus on only one factor and cannot reduce the synergistic toxic effects on cells (Z. Guo et al., 2014).

Chai et al. developed a super-assembled MOF nanozyme system (2MI-P@MSN) to simultaneously detect, image, and chelate intracellular Zn^{2+}, and scavenge ROS. This system, comprising polyethylene glycol (PEG)-modified mesoporous silica nanoparticles (MSN), can encapsulate 2-methylimidazole (2MI) and a Zn^{2+} probe (PZn), exhibiting a "turn-on" fluorescence signal for Zn^{2+} at 476 nm. 2MI chelated free Zn^{2+}, assembling ZIF-8 intracellularly at the same site. Furthermore, 2MI-P@MSN is biocompatible and non-toxic and can effectively increase the survival rate of reperfusion-injured cells from 52% to 73%, while enabling selective quantitative Zn^{2+} detection in cells (Chai et al., 2021).

5.5 Preventing cerebral ischemia-reperfusion injury

The rapid restoration of blood perfusion is crucial in IS treatment; however, reperfusion can lead to secondary CIRI. Tian et al. synthesized a multi-enzyme cascade antioxidant system (Fe2NC@Se) via the encapsulation of a double iron atom nano-enzyme (Fe2NC) within a selenium-containing MOF (Se-MOF) shell layer. The Fe_2NC@Se nano-enzymes,

exhibiting SOD, CAT, and GPx-like activities, can effectively remove intracellular ROS and inhibit the ASK1/JNK apoptosis pathway. This resulted in a reduction of oxidative damage and neuronal apoptosis post-CIRI (Ruizhen Tian et al., 2022).

Cheng et al. established integrated nano-enzymes (INAzymes) by adding hemin and GOD in ZIF-8 nanostructures, improving catalytic activity and stability. 'The dual enzyme reaction of INAzyme facilitates glucose detection and monitoring of striatal glucose changes after cerebral ischemia/reperfusion in rats (Cheng et al., 2016).

5.6 Crossing the blood–brain barrier for treatment

Penetrating the blood–brain barrier (BBB) is important in IS treatment. Although BBB can be disrupted by excessive ROS during ischemia-reperfusion in stroke, previous studies have shown that a damaged BBB persists only a few hours in the open state (X. Jiang et al., 2018; Sadeghian et al., 2019). Recent studies have reported that MOF Nanozymes possess potent anti-inflammatory and anti-oxidative properties; therefore, they can be used for the treatment of IS. Nevertheless, insufficient accumulation of MOF Nanozymes in the ischemic brain by non-invasive administration inhibits their application. Feng et al. constructed a neutrophil-like membrane-coated mesoporous Prussian blue MOF Nanozyme (MPBzyme@NCM), leveraging the natural association between inflamed brain microvascular endothelial cells and neutrophils post-stroke (Figure 5). This design improved BBB penetration and delivery of MOF Nanozymes to the ischemic brain. MPBzyme@NCM modulates microglia polarization, alleviates neuronal apoptosis, and promotes the proliferation of neural stem cells and precursors (L. Feng et al., 2021).

MOF nano-enzymes are a promising approach for stroke treatment. They can effectively alleviate oxidative stress and inflammatory responses while ensuring targeted delivery to affected brain regions. By scavenging ROS/RNS, chelating excess Zn^{2+}, and crossing the BBB, these nanozymes provide a multifaceted strategy for the treatment of IS. Their novel designs and functionalities exhibit significant potential in addressing the complex pathophysiology of stroke, making way for advanced therapeutic options in neuroprotection and recovery. A summary of the advantages and mechanism of action of MOF Nanozymes in the treatment of stroke is shown in Table 2.

6 Conclusions and future prospects of MOF-Based nanozymes

MOF-based Nanozymes have made remarkable advancements in biomedical research, offering novel solutions to address limitations such as insufficient catalytic activity and low specificity. Nevertheless, optimizing their performance and expanding their applicability is still challenging. The key areas of focus are as follows (Figure 6):

a. **Improving Catalytic Activity:** MOF Nanozymes can catalyze a limited array of reactions, including specific redox and hydrolysis reactions, unlike the diverse biochemical reactions catalyzed by natural enzymes. Composite metal MOFs, especially bimetallic ones, have shown superior enzyme-like activity compared with monometallic MOFs. Adjusting the structural ratios of these composite metals can potentially optimize catalytic systems, thereby changing morphological structure, microstructure, and overall catalytic activity.
b. **Improving Stability:** Many MOFs synthesized in organic solutions show poor stability in aqueous environments and their backbone structure is prone to damage during catalysis. Therefore, more water-stable MOFs should be developed. Approaches such as reducing MOF material size or doping with metal nanoparticles (such as platinum) can improve reusability and broaden medical applications.
c. **Co-Immobilization of Multiple Enzymes:** The trend towards adding various catalytic agents, such as natural enzymes, Nanozymes, and metal nanoparticles, is garnering attention. Such multifunctional catalysts can allow pro-cascade reactions, reduce diffusion barriers, and maximize catalytic efficiency. Nevertheless, limitations, such as large particle sizes, inhomogeneous growth, and low utilization of catalytic sites in some MOF complexes, warrant further investigations.
d. **Alleviating Immunogenicity:** Although MOF nano-enzymes have made immense progress in stroke therapy due to their multi-enzyme catalytic activity, they have been studied only in small animals and are still far from clinical translation. Nevertheless, some limitations, such as immunogenicity, clinical toxicity, and poor pharmacokinetics, are still present. Therefore, the systematic study and real-time monitoring of the pharmacokinetics, biodegradation, and physiological parameters of MOF-derived Nanozymes after administration, and the assessment of long-term toxicity for further clinical translation should be the future focus.
e. **Improving Brain-Targeting Ability:** In the present study, only neutrophil-like cell membrane-coated MOF nano-enzyme was used to improve their brain-targeting ability. However, this method targets the site of inflammation and not the brain. If inflammation is present in other parts of the body, the drug enrichment can decrease at the ischemic inflammatory site of the brain. Therefore, using other brain-targeted formulation methods such as selecting suitable brain targets, formulation design and optimization, physical stimulation and penetration enhancement techniques, chemical modification and modification, and nasal administration can become effective measures to improve the brain-targeting properties of MOF nano-enzymes.

Despite these challenges, the ongoing studies on MOF-based Nanozymes are promising. These limitations will be surmounted with the advancements in the field, making the way for widespread development and application in stroke treatment. The role of MOF-based Nanozymes in these diverse fields indicates a promising future for their use in advanced medical and biotechnological applications.

Author contributions

MC: Conceptualization, Investigation, Writing–original draft. YQ: Writing–original draft. YP: Investigation, Writing–original draft. RM: Writing–original draft. HT: Writing–original draft. ZQ: Supervision, Writing–review and editing. JM: Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Guilin Municipal Bureau of Science and Technology (20220134z), the Guangxi Clinical Research Center for Neurological Diseases (AD17129015), Guangxi Engineering Research Center of Digital Medicine and Clinical Translation, Guangxi Key Laboratory of Big Data Intelligent Cloud Management for Neurological Diseases (ZTJ2020005), Research and Innovation Base for Basic and Clinical Application of Nerve Injury and Repair (ZY21195042), Innovation and Entrepreneurship Training Programme for University Students of Guilin Medical University (S202310601070).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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