Review Article

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Recent Advances in ROS-Scavenging Metallic Nanozymes for Anti-Inflammatory Diseases: A Review

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Oxidative stress and dysregulated inflammatory responses are the hallmarks of inflammatory disorders, which are key contributors to high mortality rates and impose a substantial economic burden on society. Reactive oxygen species (ROS) are vital signaling molecules that promote the development of inflammatory disorders. The existing mainstream therapeutic approaches, including steroid and non-steroidal anti-inflammatory drugs, and proinflammatory cytokine inhibitors with anti-leucocyte inhibitors, are not efficient at curing the adverse effects of severe inflammation. Moreover, they have serious side effects. Metallic nanozymes (MNZs) mimic the endogenous enzymatic process and are promising candidates for the treatment of ROS-associated inflammatory disorders. Owing to the existing level of development of these metallic nanozymes, they are efficient at scavenging excess ROS and can resolve the drawbacks of traditional therapies. This review summarizes the context of ROS during inflammation and provides an overview of recent advances in metallic nanozymes as therapeutic agents. Furthermore, the challenges associated with MNZs and an outline for future to promote the clinical translation of MNZs are discussed. Our review of this expanding multidisciplinary field will benefit the current research and clinical application of metallic-nanozyme-based ROS scavenging in inflammatory disease treatment.

Key Words: *Reactive Oxygen Species; Nanomedicine; ROS Scavenging Nanomedicine; Metallic Nanozymes; Inflammation*

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INTRODUCTION

Inflammation is the body's defense mechanism against a variety of pathological factors such as viruses and bacteria, and it is programmed by both the innate and adaptive immune systems.[1-3] During infection, the innate immune system recognizes the unit damaged by a pathogen and activates various host cells such as neutrophils and macrophages, NK cells, mast cells, eosinophils, and basophils, which work with the host cell to mediate inflammation progression against infectious agents.[1,4-7] The adaptive immune system is more specific in terms of antigen presentation and induces effective immune responses such as cell death mediated by toxic T lymphocytes and production of specific antibodies by B lymphocytes to act against pathogenic antigens. Another advantage of the adaptive immune system is that it remembers antigens and responds to them quickly upon secondary infection.[8-11] Inflammation is divided into acute inflammation and chronic inflammation. Acute inflammatory response continues for a brief period, rapidly eliminates pathogens, and promotes inflammation resolution through tissue repair and homeostasis.[12-15] When acute inflammation is not resolved effectively, it leads to chronic inflammation, which further morphs into autoimmune or inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis, Alzheimer's disease, and atherosclerosis.[16-20] Therefore, it is important to develop therapeutically effective approaches against the aforementioned inflammatory diseases.

The ongoing anti-inflammatory therapies are based on the use of steroidal or non-steroidal drugs anti-inflam-

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matory drugs (NSAIDs), which are widely recognized as mediocrely efficient.[21,22] The limitations of these drugs include off-target biodistribution, poor bioavailability, and inability to cross biological barriers.[23,24] Recently, anti-leukotrienes, which hinder inflammatory cell recruitment to inflammatory sites, and proinflammatory cytokine inhibitors such as anti-TNF α and anti- IL-1 antibodies have emerged.[25-31] However, these treatments are inadequate for controlling the progression of complex inflammation. Therefore, the development of novel anti-inflammatory approaches to overcome these limitations with adequate efficacy is crucial.

Nanoparticles (NPs), which measure a few hundred nanometers in size, have been studied for use in anti-inflammatory treatments.[32-34] A major advantage of NPs is that they can be customized depending on specific therapeutic requirements.[35-41] NPs can easily be tuned into different sizes with adequate surface modification, as well as controlled for shape, size, and surface charge.[42,43] The synthesis of biocompatible NPs is a key approach to the development of safe drug-delivery systems.[38,44] Owing to the leaky nature of vasculature, NPs accumulate in sites of inflammation through sub-endothelial spaces. Moreover, targeting moieties can be functionalized on the surfaces of NPs to promote their active accumulation in targeted tissues to realize targeted drug delivery and therapy, which can reduce offsite toxicity and side-effects.[45-50] Various types of NPs such as liposomes, polymeric NPs, dendrimers, lipid NPs, silica NPs, quantum dots, and metallic NPs have been investigated for treating anti-inflammatory diseases. This is because these NPs can be designed for drug delivery to different biological destinations, which alleviates the challenges of systemic toxicity and rapid renal clearance associated with conventional treatments. Liposomes, which consist of lipid bilayers and polymeric vesicles, are well-established as cargo carriers for delivering NSAIDs, inhibitors, and nucleic materials.[49,51,52] However, the preparation of these NPs by subjecting them to targeting ligand modifications, drug loading, and carrier lipid encapsulation often increases their size (>100 nm), which hinders their penetration through biological barriers and easy clearance through the liver and spleen. Another drawback of these lipid and polymer nanocarriers is that they cannot be used in theranostic approaches.[43] Without modification using fluorescent dyes, metal ions, or other imaging contrast agents, these nanocarriers cannot gather any information about their own in vivo biodistribution, interaction with inflamed tissues, and mechanism of action.

Metallic NPs have emerged as a potential therapeutic model for treating inflammatory diseases. As drug delivery agents, MNPs can be tuned to different sizes to help them penetrate through various biological barriers. The high surface ratio of MNPs allows for advanced functionalization with targeting ligands, drugs, and other therapeutic agents.[53,54] MNPs have been investigated extensively for use in in vivo imaging models because MNPs possesses extraordinary physical properties such as optical, magnetic, acoustic, and electrical properties, which are useful for label-free in vivo imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), and photoacoustic (PA) imaging.[53-58] In addition, ex vivo tracking of MNPs in major organs can be performed easily by means of inductively coupled plasma mass spectrometry (ICP-MS), and their tissue and cellular distributions can be visualized using bio-transmission electron microscopy (bio-TEM) and confocal imaging systems. Therefore, MNPs are alluring candidates for bio-nano interaction research. The self-therapeutic efficacy of MNPs in treating various inflammatory diseases is noteworthy. MNPs efficiently reduce the oxidative processes in inflammatory tissue by scavenging the free radicals generated because of inflammation.[59-61] Thus, MNPs have both drug-carrying and self-therapeutic efficacy for treating various inflammatory diseases (Table 1).[45,59,60,62-92] In this review, we discuss the roles of recently reported MNPs in the scavenging of reactive oxygen species (ROS) and in anti-inflammatory activities.

TABLE 1. List of Metallic nanoparticles for the treatment of inflammatory diseases

Metallic nanoparticles	Mechanism of action	Targeted diseases	References
Manganese (Mn)	CAT and SOD mimetic nanozyme activities	Sepsis, Acute kidney injury, Diabetic wound healing, Anti-inflammatory therapy, Ischemic stroke, Neuropathic pain	45, 59, 62, 63, 64, 65, 66, 67
Cerium (Ce)	CAT and SOD mimetic nanozyme activities	Parkinson's disease, Rheumatoid arthritis, Monocrotaline-induced pulmonary arterial hypertension, Colitis, Acute liver injury, Alzheimer's disease, Stroke therapy, Diabetic ulcer wounds	68, 69, 70, 71, 72, 73, 74, 75
Prussian blue (PB)	POD, CAT, and SOD-like multienzyme activities	Ischemic stroke, Arthritis, Neuroinflammation, Inflammatory bowel disease, sepsis, Skin inflammation	60, 76, 77, 78, 79, 80, 81
Platinum (Pt)	CAT, SOD and POD-like activities	Hepatic ischemia/reperfusion injury, Vascular diseases, Chronic inflammatory diseases, Cerebral cavernous malformation disease	82, 83, 84, 85, 86, 87, 88
Ruthenium (Ru)	CAT and SOD mimetic nanozyme activities	Acute kidney injury, Liver injury	89, 90, 91, 92

ROLE OF ROS IN INFLAMMATION

ROS have classically been described as moderately reduced oxygen derivatives with strong oxidizing properties.[93-95] Phagocytic cells, which are associated with the host defense system, produce ROS that work as signaling molecules and inflammation mediators. ROS consist of both free radicals and non-free radical oxygen intermediates such as hydrogen peroxide (H_2O_2), hydroxyl radicals, superoxide, and singlet oxygens.[94,95] These molecules are the byproducts of various enzymatic reactions that occur in different cellular organelles. The ambient amount of ROS regulates cell homeostasis, while excess ROS are necessary to eliminate infectious pathogens. However, prolonged ROS secretion leads to inflammation and tissue injury.[96] Therefore, cellular antioxidants play an important role by balancing the ROS concentration and maintaining cellular functions. NADPH-oxidase-derived ROS production was initially described in the course of phagocytosis for pathogen killing through oxidative burst. Phagocytic cells such as neutrophils and macrophages rapidly produce excess amounts of ROS and stimulate protease activity, which digests the phagocytosed microbes as the first line of defense against pathogens.[96] Mitochondria-derived ROS is the consequence of mitochondrial respiration, which is associated with metabolic activities and activates inflammasomes, the NF-κB pathway, and proinflammatory cytokines such as IL-1, IL-6, and TNF-α to initiate programmed cell death and T-cell-mediated cell death.[96] ROS are considered as doble-edged swords that protect the body against infectious pathogens but damage the surrounding tissues. Therefore, ROS-scavenging therapeutics are the most essential topic of discussion in this review from the perspective of controlling and curing inflammatory diseases.

ROS-SCAVENGING METALLIC NANOZYMES IN INFLAMMATORY DISEASES

The human body uses two types of defense systems to counter oxidative stress, namely enzymatic, and non-enzymatic. The non-enzymatic defense system produces antioxidants such as glutathione, ascorbic acid, or other tripeptides that react with and neutralize ROS.[97] The enzymatic defense system is based on three major enzymes, namely peroxidase, catalase (CAT), and superoxide dismutase (SOD). These enzymes decompose nitric oxide to peroxynitrite, superoxide to water and H_2O_2, and H_2O_2 to water and oxygen (Fig. 1).[98] Multiple MNPs exhibit similar enzymatic activity and mimic the natural enzyme function, and they are called metallic nanozymes (MNZs). MNZs are highly stable under different physiological conditions such as low pH and high temperatures. Moreover, the synthesis of MNZs is facile, inexpensive, and does not require any living organism. Therefore, researchers are increasingly focusing on the development of MNZs.[97]

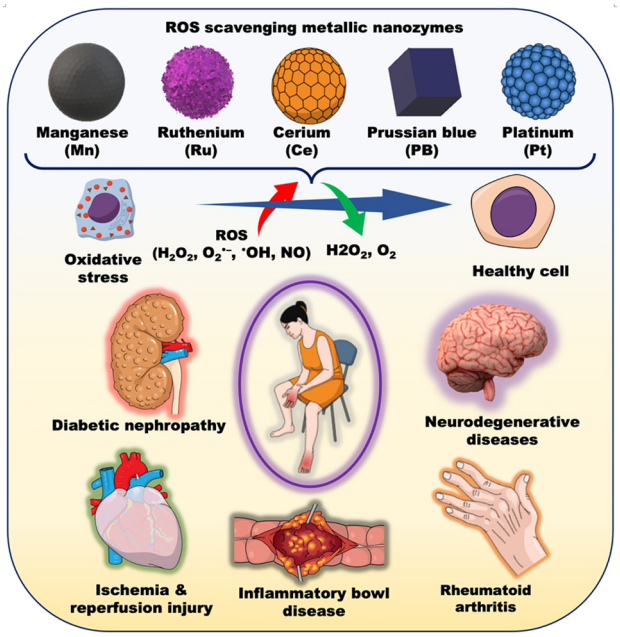

FIG. 1. A variety of metallic nanozymes (MNZs) used for the treatment of inflammatory diseases by scavenging ROS.

1. Manganese-based nanozymes

Manganese is a crucial element in the human antioxidative system, and manganese NPs afford several enzymatic activities such as superoxide dismutase (SOD), peroxidase, and catalase (CAT). Manganese nanozymes in the form of MnO_2 and Mn_3O_4 have been investigated recently for their enzyme-mimicking functions in different inflammatory diseases. Rajendrakumar et al.[59] reported that bovine serum-albumin-reduced MnO_2 NPs modified with mannose (mSPAM) efficiently targeted inflammatory macrophage cells and scavenged H_2O_2 in a lipopolysaccharide (LPS)-mediated sepsis model. A significant amount of free radical scavenging by mSPAM NPs suppressed the infiltration of neutrophils and other leukocytes in a local sepsis mice model. Moreover, LPS-induced HIF1α and Nf-κb expression was suppressed by H_2O_2 scavenging, which reduced the TNF-α and IL-6 inflammatory cytokines in serum.[59] Interestingly, mSPAM NP treatment restored the long-term potentiation (LTP) analysis (149.3±3) compared to the control group (159.6±5), where LPS treatment impaired the LTP (118.4±3). Moreover, mSPAM treatment reduced the elevated expression levels of Nf-κb and other proinflammatory markers such as COX-2 and iNOS in activated microglia cells.[59] IBA-1 immunostaining confirmed that systemic administration of mSPAM NPs reduced microglial cell activation in mice.[59] Choi et al.[45] developed an ROS-responsive, long circulating nano-micelle loaded with hydrophobic Mn_3O_4 (PTC-M) to investigate inflammation attenuation and cell apoptosis in acute kidney injury (illustrated in Fig. 2). Hydrophobic Mn_3O_4 was synthesized through the chemical reduction method and loaded onto ROS-responsive biocompatible nanocarriers, which can release the dMn_3O_4 at inflammatory sites

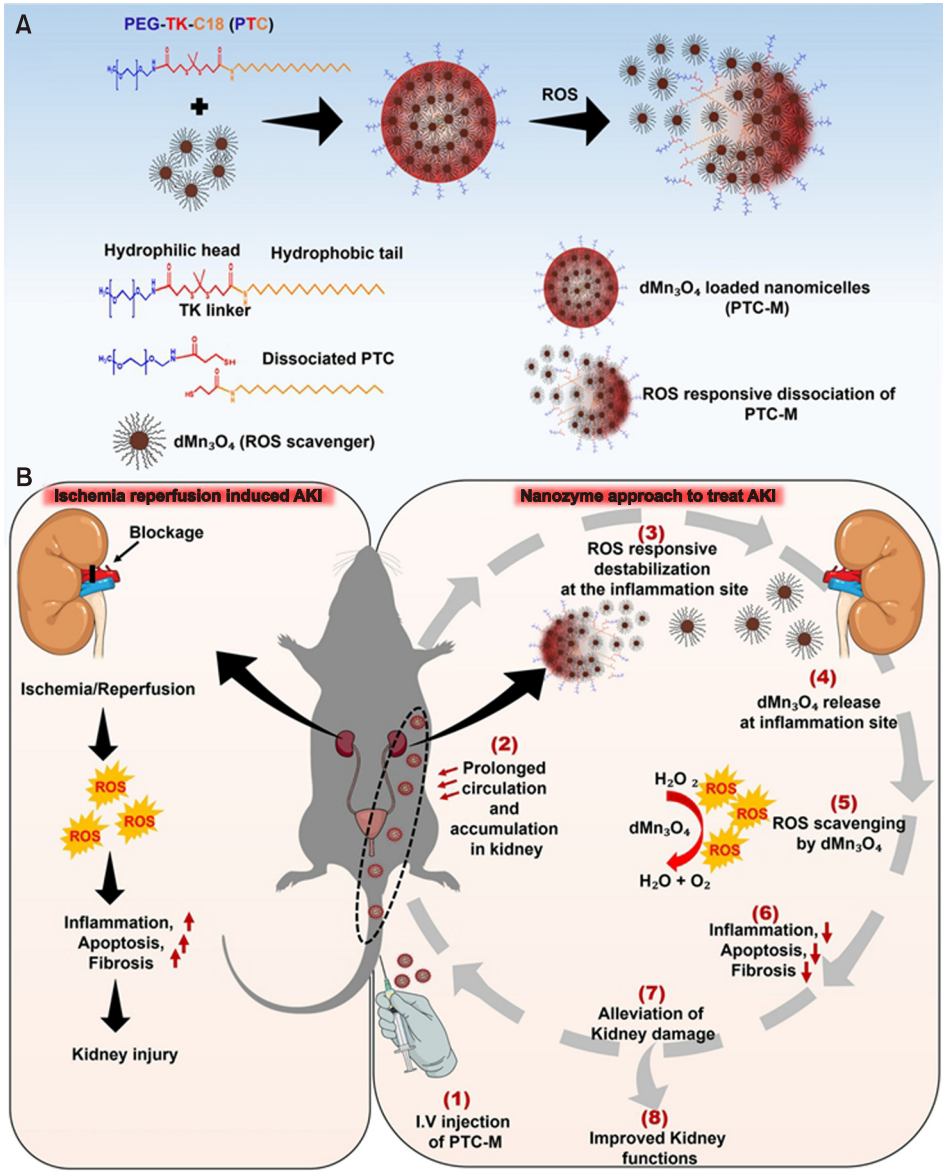

FIG. 2. Schematic diagram explaining (A) the synthesis of PTC-M NPs and (B) the mechanism of action of PTC-M NPs in acute kidney injury. PTC-M injected through the i.v. route (1); the administrated PTC-M exhibits prolonged circulation and accumulation in the kidney (2); ROS-sensitive destabilization of PTC-M (3); hydrophobic Mn_3O_4 release (4); scavenging of excess ROS by dMn_3O_4 (5); reduced inflammation (6); recovery from kidney damage (7); and improvement in basic function and condition of kidney (8). Reproduced from reference 45, licensed under CC BY 4.0.

through ROS-responsive linker breakage. A biodistribution study revealed that the PTC-M nanozyme was accumulated in the kidney after 6 h of administration and remained for 48 h with a higher accumulation rate compared to those in other organs.[45] Furthermore, PTC-M nanozyme reduced the fluorescence intensity of terephthalic acid over time, which was used to investigate the H_2O_2 elimination property of PTC-M nanozyme. The expression levels of proinflammatory markers such as interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)-α, intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM-1), and transforming growth factor (TGF)-β mRNA were alleviated after PTC-M treatment in mice. The expressions of Bax/Bcl-2 ratio and cleaved caspase-3/caspase-3 ratio in kidney tissue were analyzed to confirm the degree of renal tubular cell death.[45] In an ischemia-reperfusion injury (IRI) mice model, the Bax/Bcl-2 ratio and the cleaved caspase-3/caspase-3 ratio were elevated due to oxidative stress, and PTC-M nanozyme treatment significantly reduced these levels by reducing oxidative stress. In addition, reduced levels of phosphorylated MAPK, JNK, ERK, and P38 expressions in the PTC-M-nanozyme-treated group in the IRI model clearly proved that PTC-M nanozyme inhibited ROS-mediated apoptosis during acute kidney injury.[45] Taken together, manganese-based nanozymes are highly efficient at scavenging peroxides to resolve inflammation efficiently.

2. Cerium-based nanozymes

Cerium-based nanozymes are widely utilized in medicine owing to their antioxidative properties. Cerium nanozymes are stable in both alkaline and acidic pH and, thereby, protect against oxidants. The oxidase-like properties of cerium nanozymes depend on the Ce^{3+}/Ce^{4+} ratio, which affects the chemical reaction and stimulates antioxidant properties. Kim et al.[99] reported that HIF-1α expression

was upregulated in the joint synovium of rheumatoid arthritis owing to poor oxygen supply and excess immune cell infiltration. They developed nanoceria- and manganese-ferrite-decorated mesoporous silica NPs (MFC-MSNs) to scavenge excess ROS in rheumatoid arthritis mice model and produced sufficient oxygen, which further reduced the HIF-1α expression.[99] The MFC-MSNs continued the process of generating O_2 molecules by using hydroxyl radical intermediates produced by the manganese ferrite NPs in the Fenton reaction process. The ROS-scavenging and O_2-generating properties of the MFC-MSNs significantly alleviated hypoxia and inflammation in the joint by stimulating M2 macrophage polarization from pro-inflammatory M1 macrophages.[99] Similarly, Kalashnikova et al.[100] reported that nanoceria prepared through albumin biomineralization exhibits higher uptake in inflamed joints because multiple albumin and scavenging receptors are highly expressed in inflamed tissue, which stimulates the uptake of albumin-nanoceria (Fig. 3). In addition, secreted protein acidic and rich in cysteine (SPARC) is an extracellular matrix protein that binds to albumin and is highly expressed in RA. Albumin-nanoceria was systemically injected for RA therapy, and it showed a higher circulation time and targeted accumulation in the joint.[100] It balanced oxidant/antioxidant through ROS scavenging and polarized the proinflammatory macrophages to balance the M1/M2 ratio. A collagen-induced arthritis model was used to investigate the anti-inflammatory properties of albumin-nanoceria. The clinical score of albumin-nanoceria decreased significantly in 21 days after injection, and it was 2.4-fold lower than that of the PBS control group and almost similar to that of methotrexate (MTX) treatment, which is used for RA treatment.[100] Therefore, cerium nanozymes are potential candidates for scavenging excess ROS and reducing hypoxia in inflammation treatment.

3. Prussian blue nanozymes

Prussian blue nanozymes (PBNs) are biocompatible iron-based coordination compounds and have been approved for treating radioactive and non-radioactive exposure to thallium/cesium.[101] PBNs are excellent ROS scavengers with multienzyme-like functions, including POD, CAT, and SOD activities.[101] In recent years, PBNs have been investigated extensively for ROS scavenging and treating ROS-associated diseases such as ischemic stroke,[102] arthritis, neuroinflammation,[103] skin inflammation,[101] inflammatory bowel disease, and sepsis.[104] Mathew et al.[60] demonstrated the role of PBNs in ROS scavenging and treating bacterial infection in mice. A hyaluronic-acid-coated PB NP (HAPB) was developed, where the hyaluronic acid coating stabilized the insoluble PB and helped to target inflammatory macrophages. LPS-activated macrophages elevated CD44 expression on the surface, meaning that the cellular internalization of HAPB was high.[60] Intracellular ROS-scavenging assays confirmed that LPS treatment of the macrophage cell line increased the ROS level, which was scavenged by HAPB treatment. Furthermore, in an LPS-induced sepsis mice model, HAPB treatment scavenged the ROS and suppressed the infiltration of neutrophils and macrophages into the peritoneum.[60] In summary, HAPB is an excellent anti-inflammatory candidate for reducing the population of M1 inflammatory macrophages and the production of inflammatory cytokines. Recently, Cho et al.[81] reported that pluronic-coated PBNs (PPBzymes) are highly stable in biological buffer and can be synthesized with a uniform particle size of 204 nm. PPBzymes suppressed cartilage degradation and increased new cartilage generation in an osteoarthritis model. By specifically blocking JNK phosphorylation, which regulates inflammation and osteoarthritis pathogenesis, a local intra-articular injection of PPBzymes attenuated inflammatory reactions and prevented cartilage degradation.[81] Overproduction of reactive oxygen and nitrogen species (RONS) induces caspase-mediated brain cell apoptosis and cerebral tissue damage during ischemic stroke. Zhang et al.[102] developed hollow Prussian blue nanozymes (HPBZs) that scavenged overproduced RONS and protected neurons from apoptosis and inflammatory damages (as shown in Fig. 4). The administration of HPBZs in an ischemic model increased cerebral glucose metabo-

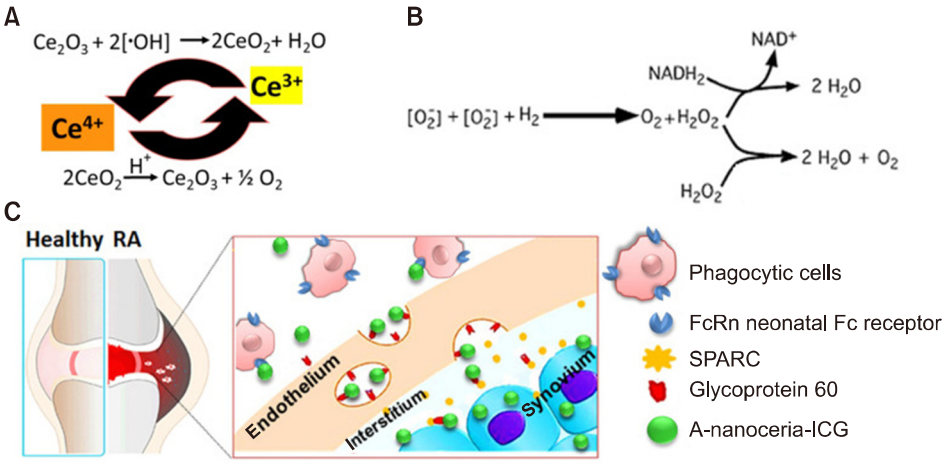

FIG. 3. Schematic illustration of (A) nanoceria valence state recycling process, (B) enzymatic action of nanoceria, and (C) albumin binding to receptors and interaction of albumin-nanoceria and inflamed cells in RA. Reproduced from reference 100, licensed under CC BY 4.0.

lism and reduced cerebral infarct volumes, which demonstrated its potential for use as a treatment option for ischemic stroke.[102]

4. Platinum-based nanozymes

Platinum nanozymes (PtNZs) replicate SOD- and CAT-mimicking enzymatic activities effectively. Similar to the biological CAT activity, PtNZs catalyze H_2O_2 to produce water and oxygen molecules. PtNZs can significantly reduce inflammation due to oxidative stress. Moreover, PtNZs inhibited the phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2), AKT, and NF-κB transcriptional activities in an LPS-treated macrophage cell line.[105] Feng et al.[85] developed a platinum coated on gold NPs (AuPt NPs) core by means of one-pot synthesis. This core exhibited an excellent ROS-scavenging property in treating kidney injury. The average size of the AuPt NPs was 57.4±9.8 nm, and they afforded both POD and CAT properties. Both Western blot and qRT-PCR results confirmed that the AuPt NPs suppressed cell necrosis and apoptosis marker genes induced by H_2O_2 treatment. The proximal tubules were protected by AuPt NPs treatment because the NPs absorbed most of the ROS produced by the mitochondria.[85] According to histological analysis, tubular damage was reduced in the AuPt-NP-treated group compared to that in the IRI control. Dihydroethidium staining, kidney SOD, and malondialdehyde level measurements were analyzed, and the results confirmed that the AuPt NPs reduced the kidney ROS level from 9.03±0.63 AU to 0.63±0.26 AU on day 1 of the treatment, which represents a significant ROS reduction.[85] In addition, the AuPt NPs reduced malondialdehyde levels and preserved kidney SOD levels. Feng et al.[85] explained that PtNPs protected old atmospheric plasma (CAP) cytotoxicity-induced mitochondrial membrane depolarization and damage by scavenging intracellular RONS. PtNZs are currently being investigated extensively for the ROS-scavenging and anti-inflammatory properties.

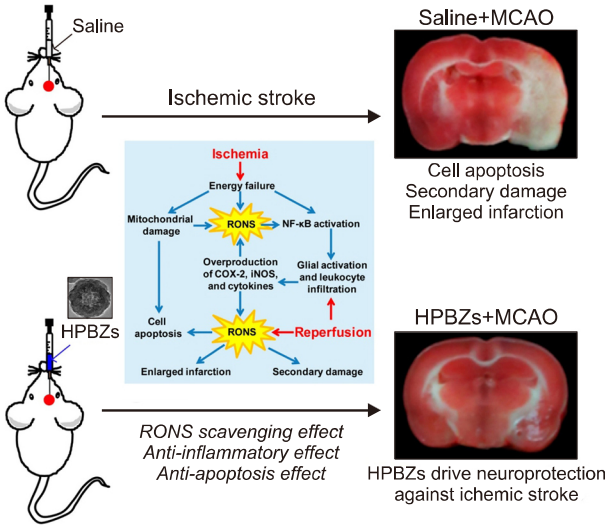

FIG. 4. Schematic representation of HPBZs-mediated ROS scavenging and neuroprotection against ischemic stroke. Adapted with permission 102 Copyright © 2019, American Chemical Society.

5. Ruthenium-based nanozymes

Ruthenium (Ru) is a transition metal element with good biocompatibility and enzymatic properties.[91] Ru-based complexes are less toxic and highly active, suggesting their suitability for use in biomedical applications.[91] The multi-enzymatic role of Ru-based nanozymes (RuNZs) in ROS scavenging has been less explored. RuNZs are biocompatible nanozymes with outstanding catalytic properties in terms of both oxygen reduction and production through CAT and SOD mimicking, respectively.[91] In 2020, Liu et al.[106] reported that ultrasmall RuO_2 NPs with an average size of 2 nm exhibited excellent antioxidant activities with minimal in vivo toxicity. Owing to the glomerular filter threshold (~6 nm), only a few metallic nanozymes can be used to treat acute kidney injury. Ultrasmall RuO_2 NPs were found to be efficient at crossing through the glomerulus and being absorbed by kidney cells (Fig. 5).[106] After systemic administration of RuO_2 NPs through the i.v. route, they accumulated in the kidney and efficiently scavenged the ROS, in addition to inhibiting ROS-mediated cell

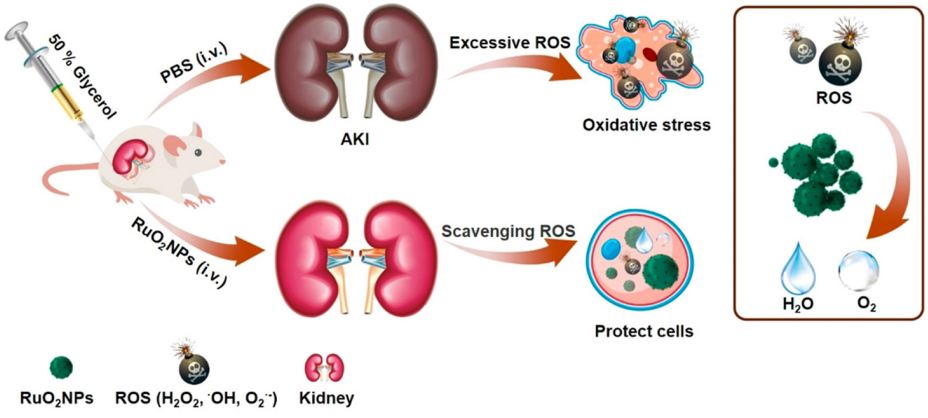

FIG. 5. Schematic representation of ultrasmall RuO_2 NPs in ROS scavenging and acute kidney disease treatment. Adapted with permission 106 Copyright © 2020, American Chemical Society.

apoptosis.[106] RuO_2 NPs treatment reduced the elevated levels of blood urea nitrogen (BUN), creatine kinase (CK), and malondialdehyde level in the AKI model. These renal execratory function markers confirmed that RuO_2 NPs scavenged ROS and alleviated renal damage in the AKI mice model.[106] In another study, Xia et al.[92] prepared RuNPs of different sizes such as ultra-small ($\approx$2 nm (uRuNP)), medium-sized ($\approx$3.9 nm (mRuNP)), and large-sized ($\approx$5.9 nm (lRuNP)). The ultrasmall RuNPs exhibited significant ROS scavenging and upregulated the regulatory T-cells in a late-stage acetaminophen (APAP)-induced liver injury (ALI) model, which highlighted the role of NP size in the ROS scavenging process. The sRuNP treatment reduced the HMGB1 expression and necrosis, which indicated the therapeutic effect of sRuNP during severe liver injury.[92]

LIMITATION AND FUTURE PERSPECTIVE

At present, metallic nanozymes are attracting considerable attention owing to their multifunctional properties such as bioavailability, specific targeting, and enzymatic activities for ROS scavenging. Although there are many ongoing studies and various studies have already reported the efficient experimental therapeutic results of metallic nanozymes in inflammatory diseases, several limitations need to be addressed. A major concern is the potential toxicity of the metallic NPs. In cellular compartments, metals form complexes with intracellular sulfur, oxygen, and nitrogen molecules and interfere with the cellular metabolic process, which leads to cell death. Excretion of larger metallic NPs is another disadvantage that leads to their deposition in excretory organs and causes tissue damage. Clinical experiments have demonstrated that treatment with metal complexes induced various health problems and side effects such as vomiting, anemia, and respiratory problems.

Despite these clinical reports on metal toxicity, there is a need for extensive preclinical and clinical studies to optimize the best metal composition for treating inflammation. In preclinical studies, it has been found that different sizes, shapes, and surface coatings regulate the toxicity of metallic NPs. These metallic nanozymes are easily decomposed to their ionic forms in redox environments, and in this manner, are released from the body rapidly. Researchers should conduct extensive preclinical investigations before entering clinical trials. Multiple surface coatings such as biocompatible polymer coating and multiple targeting ligands can affect metal toxicity. The biomineralization of metals can be a game changer for clinical use because of the resulting biocompatibility. Strategic collaboration between health institutes and pharmaceutical industries is required to establish collegial objectives pertaining to the clinical translation of metallic nanozymes because metallic nanozymes hold great potential in terms of ROS-scavenging properties and inflammation resolution.

CONCLUSION

The studies summarized in this review emphasize recent advances in nanotechnology achieved by using metallic nanozymes to scavenge excess ROS during inflammation. A certain amount of ROS is necessary for cellular homeostasis, but ROS overproduction that is unchecked by the antioxidant defense mechanism can lead to severe inflammation and tissue damage. In our opinion, MNZs act as synthetic antioxidants to trap and scavenge the excess ROS during inflammation and protect against tissue damage. We have discussed the different mechanisms of action of MNZs-based ROS scavenging. The enzyme-mimicking properties of noble metals can be explored carefully for devising various inflammation therapeutic modalities. Our basic understanding of the enzymatic action of metallic NPs has increased remarkably. Nonetheless, the challenges associated with metal toxicity need to be explored and addressed in the future. Therefore, upcoming studies should aim to achieve broad applications of metallic nanozymes for treating inflammatory diseases.

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CONFLICT OF INTEREST STATEMENT

None declared.

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