Reactive-oxygen-species-scavenging nanomaterials for resolving inflammation

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ABSTRACT

Reactive oxygen species (ROS) mediate multiple physiological functions; however, the over-accumulation of ROS causes premature aging and/or death and is associated with various inflammatory conditions. Nevertheless, there are limited clinical treatment options that are currently available. The good news is that owing to the considerable advances in nanoscience, multiple types of nanomaterials with unique ROS-scavenging abilities that influence the temporospatial dynamic behaviors of ROS in biological systems have been developed. This has led to the emergence of next-generation nanomaterial-controlled strategies aimed at ameliorating ROS-related inflammatory conditions. Accordingly, herein we reviewed recent progress in research on nanotherapy based on ROS scavenging. The underlying mechanisms of the employed nanomaterials are emphasized. Furthermore, important issues in developing cross-disciplinary nanomedicine-based strategies for ROS-based inflammatory conditions are discussed. Our review of this increasing interdisciplinary field will benefit ongoing studies and clinical applications of nanomedicine based on ROS scavenging.

1. Introduction

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), one-electron *in vivo* reduction products of oxygen compounds [1,2], are involved in various biological phenomena and play significant roles for multiple physiological functions [3]. For developing organisms, the inherent biochemical characteristics of ROS/RNS are mechanistically vital. However, the excessive production of ROS/RNS leads to oxidative stress, which is related to multiple inflammatory conditions [2,4].

Inflammation refers to a number of complex interactions between soluble factors and cells that occurs in damaged tissues after infection and/or injury [5]. Under normal conditions, during the initial recovery stage, inflammation responses provide a defense against interference from external microorganisms and promotes phagocyte degeneration of damaged tissue. However, uncontrolled inflammation, such as that occurring in diabetes, inflammatory bowel disease (IBD), atherosclerosis, neurodegenerative disease, and rheumatoid arthritis, limits recovery by tissue damage [6]. Non-resolving inflammation is a considerable medical

burden compared with any other condition, e.g. diabetes, which is responsible for 1.7 % of deaths worldwide, and accounts for at least 10 % of hospitalization costs every year [7]. In the United States, IBD incurs annual estimated costs of >$1.1 billion [8]. Atherosclerotic patients in the United States can face costs of up to $14,000 per year [9].

Over the past century, researchers have worked together to investigate ROS/RNS, especially ROS, and potential redox chemistry, leading to viable therapies for inflammation. For excessive inflammatory reaction, ROS can aggravate local tissue damage and cause chronic inflammation [10]. Hence, for inflammatory diseases, scavenging ROS with antioxidants represents a feasible therapeutic strategy. However, the transience and reactivity of ROS and unpredictability of related biological processes is quite problematic. In the field of ROS-targeted therapeutics, a significant limitation concerns the development of methods for limiting the ROS concentration to within expected limits, thus initiating therapeutic effects.

Significant advances in nanotechnology, particularly those in nanochemistry and nanomanufacturing, have allowed biomedical

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nanotechnology to revolutionize pharmaceutical and biotechnology industries, leading to considerable progress for antioxidant therapy. Many nanomaterials, such as nanoparticulate C [11], Se [12], Ce [13], Pt [14], Cu [15], redox polymers [16], and polyphenols [17], with unique ROS-scavenging properties have been prepared with the aim of moderating inflammatory ROS response. Nanotechnology that combines material science with ROS chemistry and biology has provided novel therapeutic strategies for regulating the ROS content associated with different biological situations, thereby facilitating the treatment of ROS-related diseases. Such strategies are highly feasible owing to the predictability of chemical synthesis; however, multiple aspects of the properties characterizing nanomaterials and their behaviors in biological media remain unclear.

In this article, we provide a comprehensive overview of the anti-inflammatory use of nano-antioxidants by discussing the molecular and pathological mechanisms of oxidative stress and the role of this stress in both cell and tissue damage. Then, for certain nanomaterials, we discuss the mechanisms governing ROS scavenging. Moreover, we discuss the important interdisciplinary scientific issues of ROS-based-inflammation resolution and nanomedicine with emphasis on the applications in the biomedical field and recent advances in treating inflammatory diseases. Finally, based on ROS scavenging, we consider the challenges and potential of nanomedicine. We hope that this article will provide a convenient reference for future fundamental research and clinical application.

2. Oxidative stress and inflammation

Oxidative stress, triggered by ROS/RNS overload, contributes to multiple biological processes such as aging, inflammation, and apoptosis. Commonly, ROS are composed of superoxide radical species ($O_2 \cdot^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\cdot OH$), whereas RNS are composed of nitrite (NO_2^-), nitrate (NO_3^-), and peroxynitrite ($ONOO^-$). Inflammatory cells, such as neutrophils and macrophages, are the primary ROS/RNS releasing cells [2,18].

Originally, ROS were produced with the electron transport chain in mitochondria. The production process started with the one-electron reduction of O_2 molecules for generating superoxide radical($O_2 \cdot^-$) ion, which can be produced by NADPH oxidase (NOX). $O_2 \cdot^-$, which is short-lived, is unable to cross the barrier of the cell membrane and is converted to H_2O_2 by superoxide dismutase (SOD). H_2O_2, similar to $O_2 \cdot^-$, is unstable and short-lived; however, it has the ability to cross the cellular membrane. H_2O_2 can be produced by endoplasmic reticulum oxidase 1(Ero1) through transporting the electron to O_2 in the endoplasmic reticulum [19]. A hydroxyl radical ($\cdot OH$) was produced in the reaction between H_2O_2 and transition metal Fe^{2+} (Fig. 1). At the same time, nitric oxide (NO) can be generated by nitric oxide synthase enzymes (NOS). Furthermore, $O_2 \cdot^-$ can result in peroxynitrite ($ONOO^-$), nitrite (NO_2^-), nitrate (NO_3^-) when NO is in excess production. Under physiological conditions, $ONOO^-$ undergoes protonation and homolytic cleavage to produce free radicals $HO \cdot$ and nitrogen dioxide ($NO_2 \cdot$) with high toxicity, which cause damage to proteins [2,20].

An oxidative stress induces multiple changes in organisms. Such stresses result in damage to various cell components (including proteins, lipids, and DNA [21]) that are involved in the homeostasis of redox reactions and signal transduction. This damage leads to cell dysfunction, cell death, and ultimately disease [22]. Several studies demonstrated that an oxidative stress hinders patient recovery from numerous diseases. These include malignant diseases (e.g. colon cancer and breast cancer) [23], chronic inflammation diseases (e.g. diabetes mellitus, chronic obstructive pulmonary disease, and IBD), ischemia/reperfusion (I/R) injury, autoimmune diseases (e.g. rheumatoid arthritis), neurodegenerative diseases (e.g. Alzheimer's disease and amyotrophic lateral sclerosis), and cardiovascular diseases (e.g. atherosclerosis) (Fig. 2) [24].

Inflammation and ROS are characterized by a mutually synergistic relationship. For acute inflammation, neutrophil or macrophage-derived ROS will lead to damaged cell apoptosis, thereby promoting recovery. However, for chronic inflammation, ROS can upregulate the TNF-TNFR inflammatory pathway (Fig. 3) [25]. When cytoplasmic domain of TNFR interacts with RFK and p22phox, NOXs are activated. Then ROS are generated by converting extracellular O_2 to $O_2 \cdot^-$.

Additionally, inflammation and RNS are also characterized by a mutually synergistic relationship. In TNF signaling, the binding of TNF to TNFR through an RIPK1–TAB–TAK1 complex subsequently triggers NF-κB and AP-1 transcription. After IKB phosphorylation, NF-κB, another significant inflammatory factor, is separated from the NF-κB/IKB complex [26]. Furthermore, AP-1, which is an inflammation-related factor [27], is activated by the MAPK (ERK, JNK/SAPK, and p38) pathway [28]. Subsequently, both NF-κB and AP-1 enter the nucleus, and their
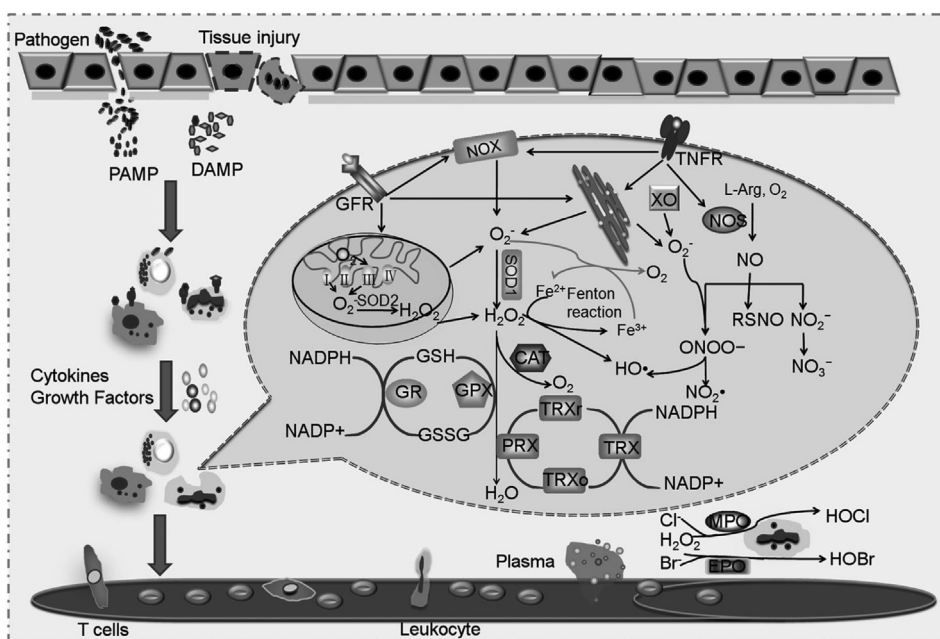

Fig. 1. Intracellular reactive oxygen species (ROS)/reactive nitrogen species(RNS) formation [2]. The formation of three primary ROS species (including $O_2 \cdot^-$, H_2O_2, and $\cdot OH$) and RNS species (NO_2^-, NO_3^-, and $ONOO^-$) Copyright 2015, John Wiley and Sons Inc.
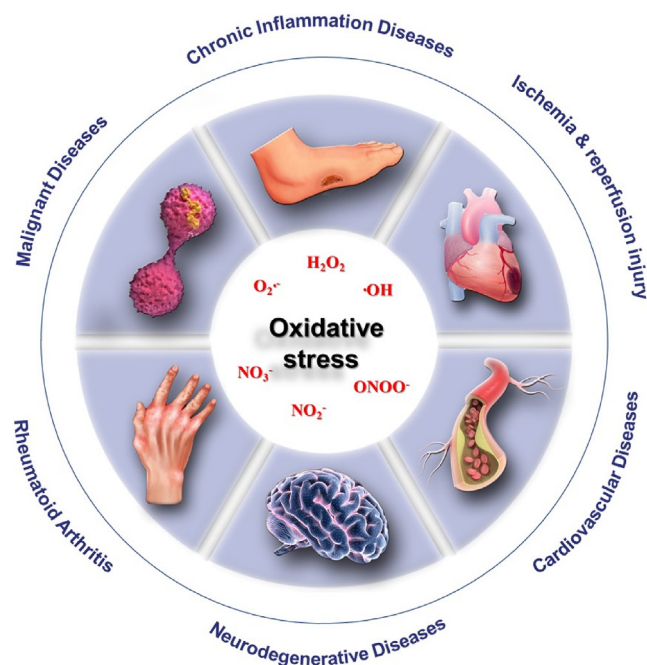
Fig. 2. Oxidative-stress-related diseases.

downstream inflammatory genes are invoked [29]. NF-κB will drive the expression of inducible nitric oxide synthase (iNOS/NOS2), which can give rise to NO$\bullet$ generation. The NO$\bullet$ can be the antioxidants to ROS but at the cost of continuously accumulated RNS. In this case, a feedback loop of antioxidants (HO-1 and H-ferritin) is stimulated.

Furthermore, high levels of ROS/RNS results in mutagenesis (such as antioxidant gene-GPx4), tumor invasion, and eventually neoplasia. A persistent inflammatory response stimulates inflammatory cells (neutrophil and macrophage), and consequently, the continuous production of ROS/RNS [30]. Accordingly, oxidative stress leads to sustained inflammatory reaction, which in turn leads to persistent ROS/RNS

production, thereby resulting in a self-perpetuating cycle.

3. ROS-scavenging nanomaterials that promote oxidative damage repair and mechanisms governing this repair

Multiple manufactured nanomaterials can neutralize excessive ROS and mitigate inflammatory diseases. Both pharmaceutical and biotechnology industries have been significantly altered by applying nanotechnology in biomedicine, leading to significant progress in the field of antioxidant therapy. This has presented methods of overcoming the limitations related to traditional antioxidants (such as vitamin C and *N*-acetylcysteine) and developing new antioxidants [31]. Importantly, nanotechnology can alter the pharmacokinetics of natural antioxidant molecules and protect these molecules from harsh pressure and low pH conditions. Compared with natural antioxidants, nano-antioxidants exhibit higher antioxidant stability and tolerance to harsh microenvironments. Furthermore, nanomaterials mimicking enzymatic activities, such as those with SOD- and/or catalase (CAT)-like activities, have recently emerged as powerful radical scavengers. Nano-antioxidants can be surface-functionalized to obtain target-specificity and/or improved water solubility [32].

Based on their different operating mechanisms, ROS-scavenging nanoparticles (NPs) can be divided into three categories (Fig. 4): enzyme-like NPs (nanozymes), free-radical trapper NPs, and redox ROS-scavenging NPs. Next, we will summarize the latest application progresses of these ROS-scavenging nanomaterials in the therapeutics of oxidative stress–induced diseases. The relevant highlights of representative ROS scavenger were shown in Table 1.

3.1. Nanozymes

3.1.1. Cerium nanoparticles

CeO$_2$ NPs, referred to as nanoceria or ceria NPs, exhibit significant pharmacological potential owing to their antioxidant properties. Their ROS-scavenging capacities are attributed to Ce^{3+} ions in CeO$_2$ and mimic biological antioxidants. In its oxide forms, Ce^{4+} and the less stable Ce^{3+}, coexist, thus forming a redox couple responsible for the catalytic activity of the material. The reduced positive charge of Ce^{3+} is compensated by a
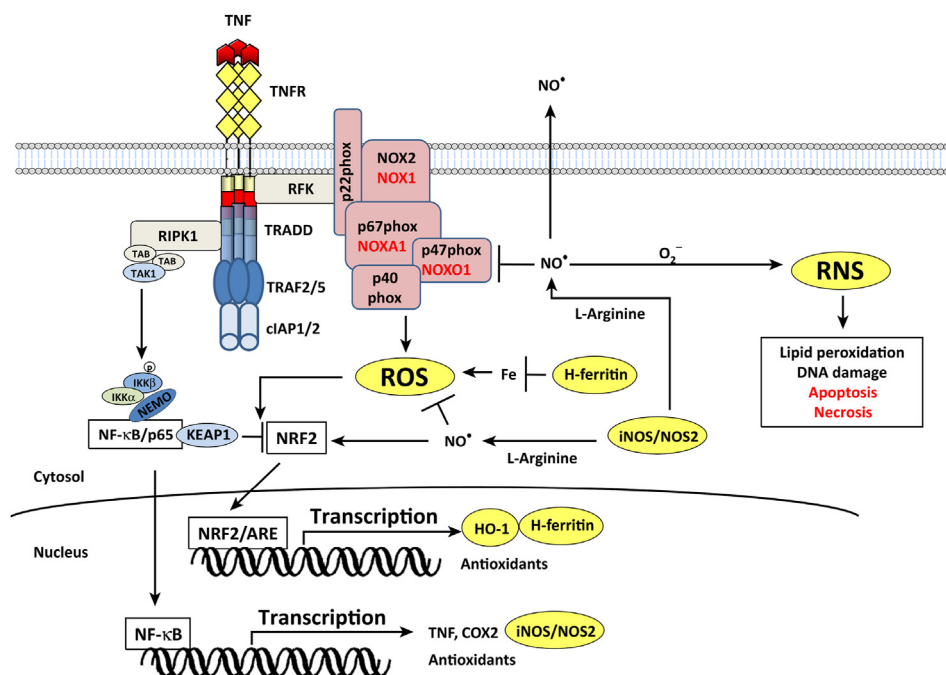

Fig. 3. Reactive oxygen species (**ROS**)/**reactive nitrogen species (RNS) and inflammation** [25]. The mutually synergistic relationship between ROS/RNS and inflammation (Copyright 2016, Elsevier Ltd.).
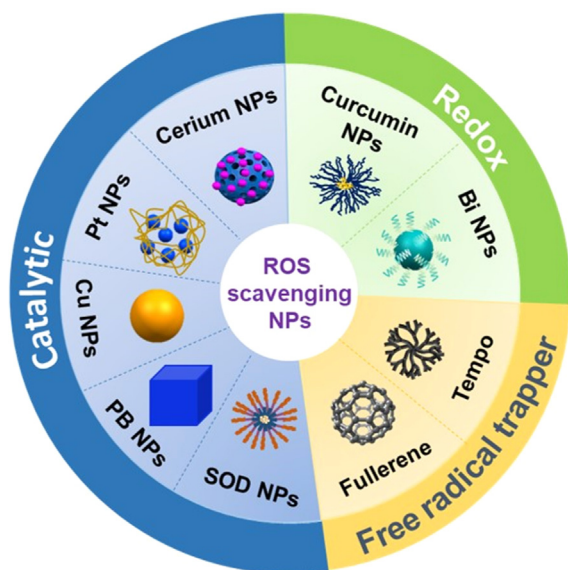
Fig. 4. Reactive-oxygen-species-scavenging nanoparticle classifications.

corresponding number of oxygen vacancies [31]. The Ce^{3+} ion concentrations and oxygen vacancies on the surface of ceria are higher than those in the bulk material. Thus, with increase in the surface area-to-volume ratio, the density of Ce^{3+} ion increases and the redox activity is enhanced [33]. Ceria NPs scavenge free radicals by reversibly binding oxygen and the transformation between Ce^{3+} and Ce^{4+} on the surface of particles. Ceria NPs exhibit SOD- [33] and CAT-mimetic activities (Fig. 5A) [34], thus protecting cells against the most abundant ROS, such as $O_2 \cdot^-$, $\cdot OH$, and H_2O_2.

Previous studies demonstrated that cerium NPs, with surface oxygen vacancies that scavenge free radicals [37,38], can be internalized by monocytes. In this manner, nanoceria can modulate intracellular ROS levels, particularly when the monocytes are activated [39]. This prevents the release of excess ROS from one of its primary sources. Ceria NPs can perform ROS scavenging when assembled on a TiO_2 substrate considering the shape of fullerene-like structures [40]. Zhao et al. reported that ceria NPs grown *in situ* on montmorillonite (MMT) can effectively target and scavenge excess ROS from inflammatory sites, thus reducing inflammation at the colonic lesions. Furthermore, CeO_2@MMT can repair impaired intestinal epithelial barrier and adjust the partly immunological surroundings of lesion sites. Thus, pro-inflammatory macrophage (M1) and cytokine (e.g. IL-1β, IL-6, and iNOS) levels are simultaneously downregulated and the anti-inflammatory macrophage (M2) and cytokine (e.g. IL-10) levels are significantly upregulated (Fig. 5C) [36]. The suppression of ROS-triggered inflammation by ceria-NP scavenging of ROS can inhibit the translocation of the P65 NF-κB subunit. This suggests that changes in the phenotype of microglia from the pro-inflammatory M1 to the anti-inflammatory M2 polarization can be influenced by controlling the NF-κB pathway *via* ceria NPs. Immunomodulation methods based on the M2 polarization of microglia through ceria NP inhibition of ROS have neuroprotective effects and provide a novel treatment for Alzheimer's disease (Fig. 5B) [35]. Kim et al. prepared mesoporous silica NPs doped with manganese ferrite and cerium NPs (MFC-MSNs) have a synergistic effect on O_2 generation and ROS removal, resulting in the effective polarization of M1 to M2 macrophages in vitro and in vivo. MFC-MSNs were intravenously administered to a rat rheumatoid arthritis model; this treatment reduced the hypoxia, inflammation, and pathological characteristics of joints [41]. Thus, ROS-scavenging NPs can reduce inflammation by targeting macrophage polarization. Other studies on CeO_2 NPs have revealed that these NPs inhibit oxidative stress–induced cell apoptosis of the central nervous system in neurodegenerative disease [42,43].

In diabetes mellitus, nanoceria play an important role in ROS scavenging. The mechanisms through which the topical application of water-soluble cerium NPs promote full-thickness wound healing in mouse skin involve the enhancement of the proliferation and migration of fibroblasts, vascular endothelial cells, and keratinocytes. The cellular uptake of nanoceria decreases ROS-induced cell death by eliminating intracellular ROS and blocking H_2O_2-activated apoptosis pathways. A study of wound healing in rodents revealed that nanoceria treatments promote skin closure and revascularization [44]. Chronic wounds, such as diabetic ulcer wounds are more susceptible to infection, leading to oxidative stress. ROS can inhibit the change of chronic wound from inflammation condition to proliferation condition, causing an inflammatory state. MoS_2–CeO_2 NPs, which have both photothermal antibacterial property and antioxidant property, can kill bacteria by scavenging excessive ROS within diabetic ulcer wounds, promoting cell migration and chronic wound healing [45].

In nerve cells, high glucose concentrations can induce considerable amounts of ROS. Accordingly, CeO_2 and Y_2O_3 NPs have been explored for combination therapy aimed at protecting nerve cells from glucose toxicity. CeO_2 and Y_2O_3 NPs improve the survival rate of undifferentiated PC12 cells under glucose-induced oxidative stress. These NPs can lead to reductions in ROS production, lipid peroxidation (LPO), and expression of the apoptosis-related genes Bax and caspase-3 proteins. Both NPs increase the expression of total thiol molecules (TTMs) and Bcl-2 proteins. Therefore, during the early stages of diabetes, this cytoprotection can prevent neuropathy [46].

Moreover, photoreceptor cells can suffer from radiation-caused eye disease, which is accompanied by a high rate of cellular oxygen metabolism and leads to the continuous exposure of these cells to the high concentrations of toxic reactive oxygen intermediates (ROIs). Chen et al. designed hollow mixed-valence cerium NPs to remove ROIs, and their results demonstrated that nanoceria prevent the increase of intracellular ROI concentration in rat retinal primary cell cultures and prevent vision loss because of light-induced photoreceptor cell degradation in vivo. This shows that nanoceria may effectively inhibit ROI-induced cell death, which may be is related to retinitis pigmentosa, macular degeneration, and other blinding diseases [47]. Furthermore, Ni et al. reported that ceria NPs can relieve the clinical symptoms of hepatic I/R injury, which is the primary cause of pressure ulcers, by eliminating ROS and suppressing the activation of Kupffer and monocyte/macrophage cells. Consequently, the release of pro-inflammatory cytokines is eliminated and the recruitment and the infiltration of neutrophils is reduced, thereby alleviating subsequent inflammatory reactions involving the liver [48].

3.1.2. Platinum nanoparticles

In synthetic chemistry, Pt is as a catalyst for hydrogenation and oxidation reactions and is clinically used for chemotherapeutic drugs such as cisplatin. Studies demonstrated that Pt can catalyze the conversion of $O_2 \cdot^-$ to H_2O_2 and H_2O_2 to H_2O and O_2 and is, therefore, considered a candidate SOD/CAT mimic for treating oxidative stress [49]. Kim et al. demonstrated that the C-terminal of the HIV-1 TAT fusion protein is linked to a peptide with a high affinity for Pt. After binding, Pt improves the endocytosis of cells and produces a similar strength of antioxidant effect at a concentration of 1% that of the corresponding unconjugated nano-Pt. This results in higher bioavailability and lower toxicity than the prebinding levels. TAT-Pt NPs can improve the survival rate of nematodes under acute oxidative stress induced by paraquat and chronic endogenous ROS, thus exhibiting potential therapeutic value for chronic inflammatory diseases [50].

Pt NPs, as an excellent mimetic enzyme, exhibit high catalytic performance, which have been used as a nanomotor to improve the effectiveness of disease treatment. Wu et al. reported a nanomotor containing Pt NPs, clarithromycin, and calcium peroxide (CaO), and the driving force of the nanomotor came from the local concentration gradient of oxygen (O_2) produced via the decomposition of H_2O_2 by Pt NPs. The results showed that the nanomotor could efficiently neutralize gastric

Table 1

Summary of the representative reactive-oxygen-species (ROS)-scavenging nanomaterials.

Materials	Working mechanisms	Indications	Ref.
CeO_2 NPs	SOD- and CAT-mimetic nanozyme activities	Colitis; acute liver injury; stroke therapy; Alzheimer's disease; monocrotaline-induced pulmonary arterial hypertension; diabetic ulcer wounds; Parkinson's disease; rheumatoid arthritis	[36,41,45, 119–123]
Pt NPs	POD-, CAT-, and SOD-like nanozyme activities	Chronic inflammatory diseases; vascular diseases; cerebral cavernous malformation disease; hepatic ischemia/reperfusion injury	[50,124–126]
Cu-based NPs	POD-, CAT-, SOD-, and glutathione-like enzyme activities	Parkinson's disease; kidney and liver injury; inflamed wounds; enteritis and wound healing; caries	[15,56,57,127, 128]
PB NPs	POD-, CAT-, and SOD-like multienzyme activities	High glucose contents, and oxygen glucose deprivation and reperfusion; acute pancreatitis; dextran sulfate sodium-induced colitis; brain diseases; inflammatory bowel disease	[16,59–62]
SOD-containing NPs	SOD enzyme activity	Brain ischemia–reperfusion injury; colitis; testicular oxidative stress; myocardial ischemia–reperfusion injury; neuroprotective	[63,65,129–131]
TEMPO	Capture ROS via the single electron on nitroxide	Polycystic ovary syndrome; cerebral cavernous malformation vascular disease; liver injury; osteoarthritis; colitis; atherosclerosis	[70,71,73, 132–134]
Fullerene	Capture ROS via conjugated double bonds	Intestinal injury; diabetes-related complications; inflammatory bowel disease; liver cirrhosis;	[79–81,132,135]
Curcumin-based NPs	Redox-activity due to low O–H bond dissociation energy	Peripheral arterial disease; cardiac ischemia–reperfusion injury; muscles of peripheral artery disease; wound healing; inflammation-induced obesity and metabolic diseases	[136–141]
Bilirubin NPs	Scavenging $O_2\bullet-$, H_2O_2, and $\bullet OH$ via an ROX-initiated redox reaction	Colitis and ulcerative colitis; hepatic ischemia–reperfusion injury; chronic inflammatory airway disease of asthma; pulmonary fibrosis	[100,142–145]
PDA NPs	Scavenging $O_2\bullet-$, H_2O_2, and $\bullet OH$ via redox chemistry of polycatechol structure	Periodontitis; porous bone scaffold transplantation; wound healing; age-related macular degeneration; acute kidney injury	[105,107, 146–148]

acid and concurrently release drug to attain well-curative effect with non-toxicity [51].

3.1.3. Cu-based nanoparticles

Cu occurs in phase II detoxification enzymes such as superoxidase and glutathione as well as enhances the activity of SOD and other enzymes, thus improving the body's ability to scavenge free radicals. Moreover, in exerting its antioxidant effect, Cu affects certain signal pathways in the body such as the nuclear factor E2-related factor signaling pathway and the CDK4-mediated mitochondrial signaling pathway. Through this effect, the body's dynamic balance is maintained and inflammatory diseases are prevented [52,53].

Furthermore, metal–organic frameworks (MOFs) show promise as antioxidant nanomaterials. The highly porous structures of MOFs allow the exposure of free radicals to active sites in nanostructures, thereby improving the catalytic activity of these radicals. The development of MOF-based enzyme mimics has recently been reported, e.g. a peroxidase (POD) mimic was obtained by incorporating Cu^{2+} into MOFs [54,55].

Recently, we reported ultrasmall $Cu_{5.4}O$ nanoparticles ($Cu_{5.4}O$ USNPs) with broad-spectrum ROS-scavenging and enzyme-mimicking abilities for treating ROS-related diseases (Fig. 6A). $Cu_{5.4}O$ USNPs mimic the properties of CAT, SOD, and glutathione enzymes. A very low dose (150 ng mL^{-1}) of these USNPs can lead to significant reduction in the severity of kidney and liver injury and promote wound healing (Fig. 6B). Furthermore, the renal clearance of such USNPs is rapid, thereby ensuring biocompatibility [15]. Subsequently, the $Cu_{5.4}O$ USNPs were loaded into the Hep-PEG hydrogel to suppress the inflammation of wounds. The heparin could efficiently capture inflammatory chemokines monocyte chemoattractant protein-1(MCP-1) and interleukin-8(IL-8) and reduce migratory activity of neutrophils and macrophages. At the same time, $Cu_{5.4}O$ USNPs, as a nanozyme, scavenged ROS to reduce oxidative stress and promoting angiogenesis. Thus, the inflammation feedback cycle was completely broken via capturing pro-inflammatory factors and scavenging ROS concurrently [56].

Hao et al. prepared uniform Cu_xO NPs (65 ± 7 nm) using Phe as a structure-directing agent. These NPs mimic the POD, SOD, CAT, and glutathione peroxidase (GPx) activities, exhibiting strong and extensive ROS-scavenging capacity, inhibiting neurotoxicity in a cell model of
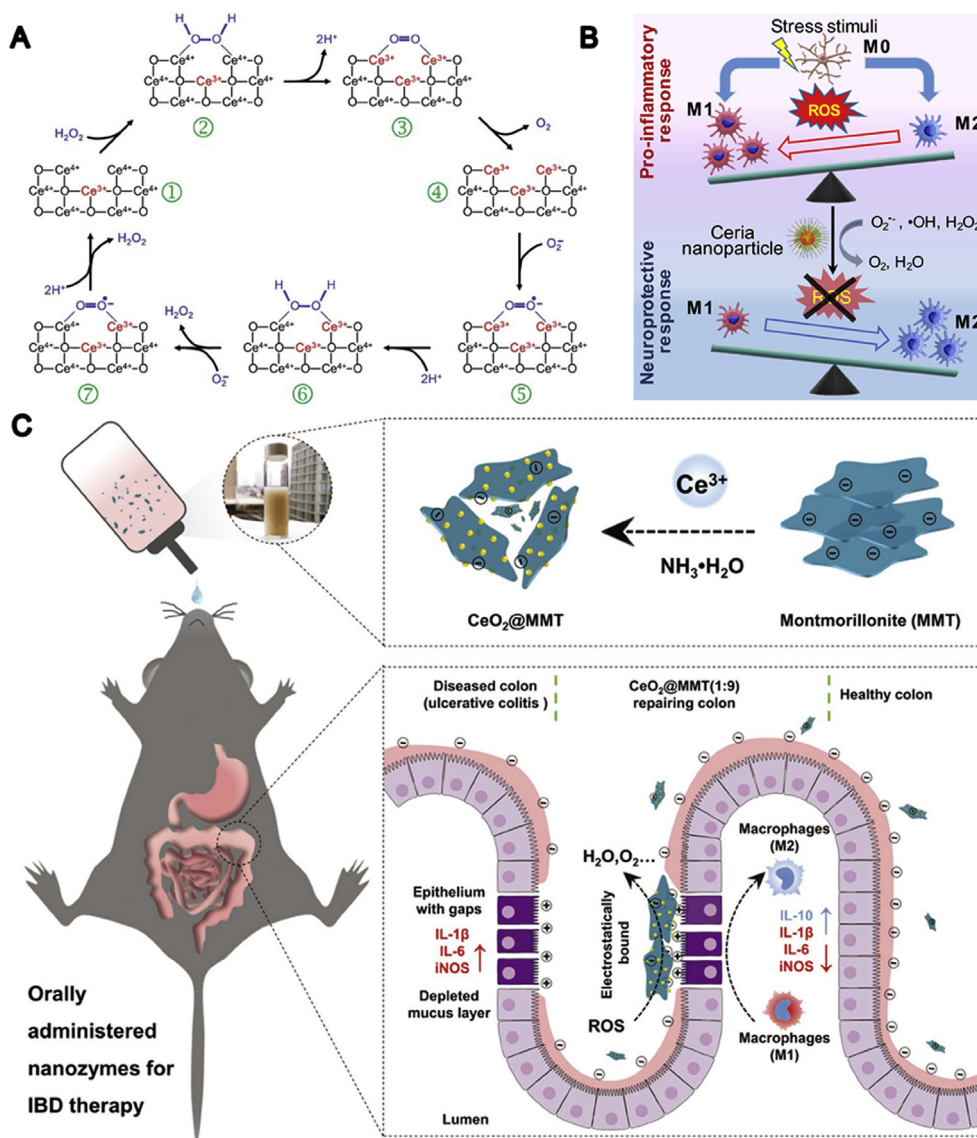
Fig. 5. (A) Reactive-oxygen-species (ROS)-scavenging mechanism of nanoceria [33]. Copyright 2011, Royal Society of Chemistry. (B) Ceria nanoparticles can change the polarization of microglia from the M1 to the M2 phenotype by scavenging stress–induced ROS [35]. Copyright 2018, Wiley. (C) Design and synthesis of orally administered CeO₂@MMT aimed at targeting an inflamed colon during the treatment of inflammatory bowel disease (IBD) [36]. Copyright 2020, Wiley-VCH Verlag.

Parkinson's disease, and reducing memory loss in Parkinson's disease mice [57].

3.1.4. Prussian blue nanoparticles

The electron transfer ability of Prussian blue (PB) NPs plays an important role in the abundant redox potential of these NPs, allowing such NPs to simulate the POD, CAT, and SOD activities in scavenging ROS [58]. Therefore, PB NPs exhibit significant potential for treating inflammatory diseases. Xie et al. explored the inherent antioxidant and anti-inflammatory mechanisms of PB nanozyme on acute pancreatitis (AP). The PB nanozyme could scavenge ROS and inhibit the toll-like receptor/nuclear factor-κB signaling pathway, which presented excellent antioxidative and anti-inflammatory abilities in decreasing inflammation and oxidative stress for ameliorate AP [59].

Zhao et al. reported that PVP-modified PB NPs exhibit broad-range antioxidant defense ability and excellent $O_2 \cdot^-$, $\cdot OH$, H_2O_2-, and OOH-removal capability. Therefore, these NPs yield significant therapeutic effects in dextran sulfate sodium-induced colitis mice without observable side-effects [60]. PB NPs possess effective antioxidative and anti-inflammatory abilities. While their application was hindered due to the lack of accumulation in inflammatory sites via non-invasive therapy.

Zhang et al. developed the neutrophil-like, cell-membrane-coated mesoporous PB NPs (MPBzyme@NCM) to achieve the purpose of non-invasive and active targeting to damaged brain through microglia uptake. The mechanism of ischemic stroke therapy by nanomaterials was the microglia polarization toward M2, decreased proliferation of neutrophils, reduced apoptosis of neurons, and the recruitment of neuronal precursors, neurons and neural stem cells. This strategy solved the major problem of short drug transmission to the damaged brain and offered an effective strategy for NP therapy in brain diseases [61]. Moreover, in ROS-production models, involving chemical agents, ultraviolet radiation, oxidized low-density lipoprotein, hyperglycemia, and oxyglucose deprivation, and reperfusion, researchers explored the ROS-scavenging abilities of PBs [62].

3.1.5. Superoxide dismutase (SOD)-containing nanoparticles

Endogenous cells use SOD to remove $O_2 \cdot^-$ and H_2O_2. Accordingly, NPs conjugated with recombinant SOD provide the effective intracellular delivery of enzymes under oxidative stress conditions while protecting enzymes in the serum from degradation.

Owing to increased amphiphilicity, the combination of SOD and NPs promotes blood–brain barrier permeability, which allows the application
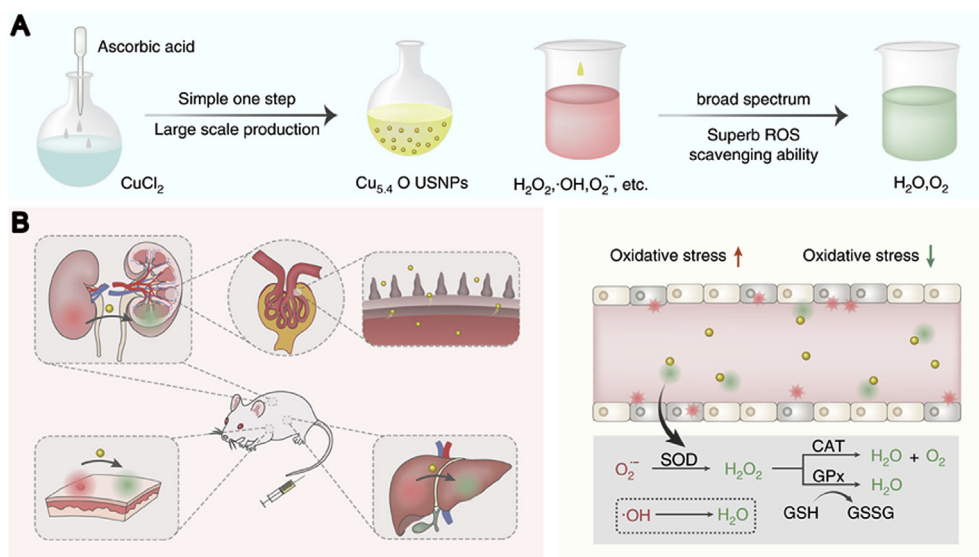
Fig. 6. Schematic of $Cu_{5.4}O$ USNPs for treating reactive oxygen species (ROS)-related conditions [15]. (A) $Cu_{5.4}O$ USNPs are synthesized using a simple and environmentally benign method. (B) $Cu_{5.4}O$ USNPs exhibit therapeutic effects against various ROS-related diseases (including acute kidney injury [AKI] and acute liver injury) and promote diabetic wound healing. Copyright 2020, Springer Nature.

of such NPs to brain I/R injury. For example, Reddy et al. used poly (D, l-lactic-glycolic acid) (PLGA) NPs containing SOD to treat rat brain I/R injury by providing sustained SOD transport, thereby improving the survival rate and neurological function [63]. During reperfusion, the infusion of SOD-containing NPs led to a considerable decrease in infarct size.

Recently, Chen et al. designed silica NPs containing the SOD His tag domain and HIV Tat domain that enhance transmembrane transport [64]. Using a novel method of drug administration, we linked the enzyme to NPs and then transferred the enzyme to cells. This transfer was followed by denaturing and refolding of the enzyme in the cell for restoring its catalytic activity. Similarly, Zeng et al. developed a method to package the antioxidant enzymes including SOD and CAT into amphiphilic wind chime- like cyclodextrin (WCC) to improve drug delivery effect without enzyme inactivation. The SOD and CAT co-loaded WCC NPs (SC/WCC) could cooperate with the ROS-scavenging effects of SOD and CAT, and efficaciously restrain inflammatory response via decreasing the expression of pro-inflammatory factor. The SC/WCC could efficaciously accumulate in inflamed colon and efficiently relieve the symptoms of colitis, which might provide an effective strategy for the treatment of other inflammatory diseases [65].

3.2. Free-radical trapper nanoparticles

3.2.1. 2, 2, 6, 6-Tetramethylpiperidinenoxyl-based nanoparticles

As a well-established ROS scavenger, 2, 2, 6, 6-tetramethylpiperidinenoxyl (TEMPO) can capture unpaired electrons from other radicals by a single electron on nitroxide, and the redox reaction switch between oxidation states of nitroxide, oxoammonium cation, and hydroxylamine [66]. The nitroxide/oxoammonium redox couple promotes the catalytic process by reversible one-electron redox reaction, and hydroxylamine acts as a hydrogen-atom donor, providing antioxidant function. TEMPO, as a membrane-permeable stable nitroxide radical that can scavenge superoxide and peroxide, undergoes Fenton reactions and radical–radical recombination [66].

Studies demonstrated that TEMPO can be used for treating various diseases [67,68]. In a hepatic I/R model, polynitroxyl albumin and TEMPO reduced ROS levels, resulting in mitigating liver injury and inflammatory reaction symptoms, particularly the reduction of intracellular adhesion molecule-1 (ICAM-1) and neutrophil accumulation [69]. Li et al. have shown that TEMPO ameliorated dehydroepiandrosterone-induced

polycystic ovary syndrome (PCOS) via attenuating oxidative stress in the gut, recovering the gut dysbiosis and adjusting the interaction of host metabolites and gut microbiota. Thence, TEMPO treatment is a promising method for PCOS [70]. Giovanna et al. explored the anti-inflammatory mechanism of TEMPO in osteoarthritis (OA). The results shown that TEMPO administration could reduce the inflammation status and oxidative stress, the generation of nitrite and pro-inflammatory mediators. Therefore, TEMPO administration was expected to be a new therapeutic approach for oxidative stress–induced inflammation [71].

In addition, TEMPO was also used to combine with other nanomaterials to enhance its antioxidant effect. Zhang et al. prepared a SOD-/CAT-mimetic nanomaterial that combines a cyclodextrin-derived material for H_2O_2 elimination with the free-radical remover Tempol (Tpl/OxbCD-NP) (Fig. 7A). For several different mouse models, orally administered Tpl/OxbCD-NP led to the significant suppression of colitis symptoms and the expression of pro-inflammatory mediators. Furthermore, the efficacy of Tpl/OxbCD-NP was reported to be better than that of free Tpl or a PLGA-based nanomaterials [72]. Hu et al. covalently coupled cyclodextrin with tempol and pinacylboronate (TPCD-NPs) to obtain a new antioxidant and anti-inflammatory NP for targeted atherosclerosis treatment with broad-spectrum ROS-scavenging ability. After intravenous injection in animals, TPCD-NPs reduced inflammation and apoptosis (Fig. 7B). The therapeutic advantages of TPCD-NPs primarily arise from the reduction in inflammation and oxidative stress along with a decrease in inflammatory cell infiltration in atherosclerotic plaques [73].

3.2.2. Fullerene

Fullerene (C_{60}) is a form of crystalline carbon with radical scavenging abilities attributed to its conjugated double bonds with good electron affinity, which makes it an excellent electron acceptor. The C_{60} can capture ROS by accepting their unpaired electron [74–76]. Studies have shown that both superoxide and hydroxyl radicals were immobilized on the fullerene surface [77] (Fig. 7C). Accordingly, fullerene NPs can inhibit cell toxicity, mitochondrial damage, and LPO [78]. Because fullerene is insoluble in water and biological environment, derivatized water-soluble fullerenes have been designed to improve ROS-scavenging ability to target cells and tissues. Tang et al. proved that water-soluble fullerene could reduce cellular ROS levels and oxidative stress state to ameliorate the immune response and intestinal injury [79]. Hydrated fullerene NPs have been applied for treating diabetes-related
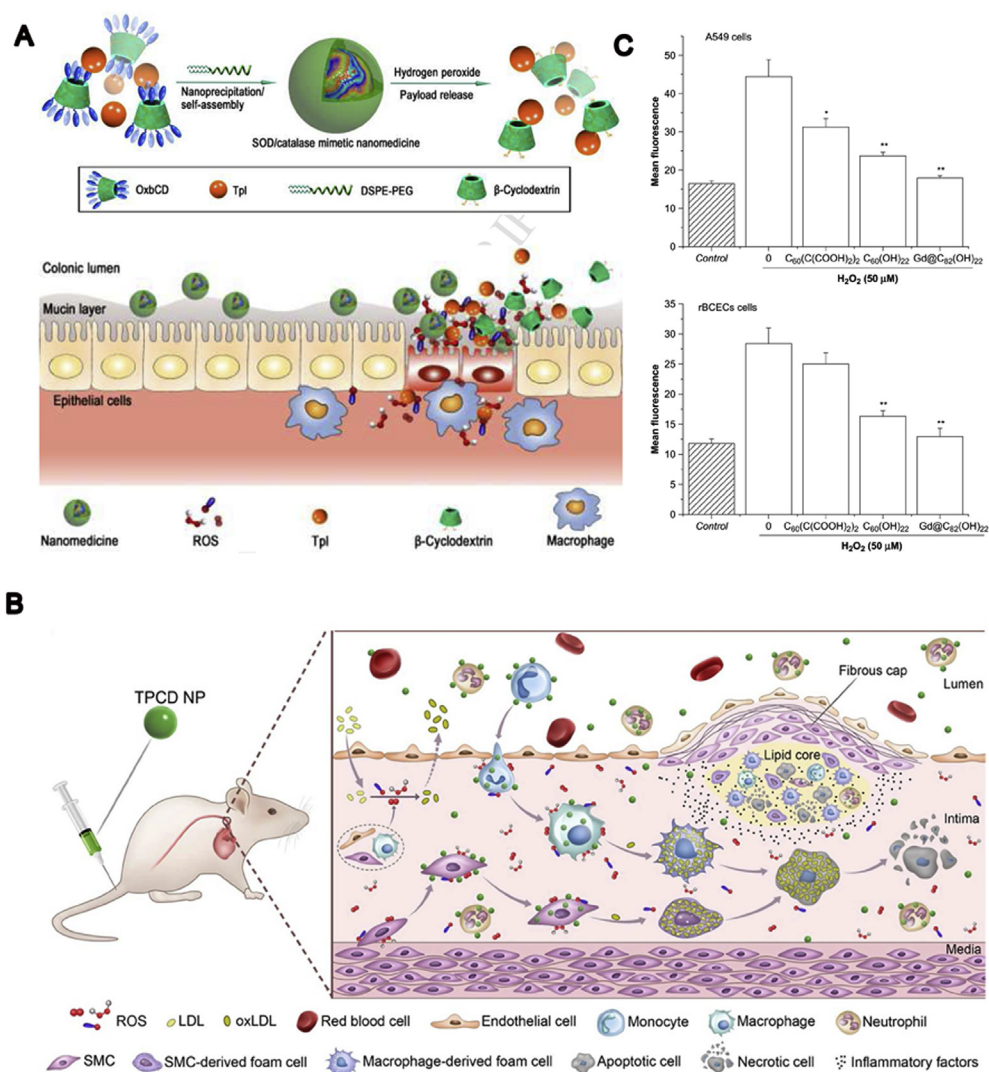
Fig. 7. (A) Schematic of the composition and engineering of Tpl/OxbCD nanoparticles (NPs) and their targeted therapy of colitis [72]. Copyright 2016, Elsevier. (B) Illustration of targeted atherosclerosis treatment realized by eliminating reactive oxygen species through the intravenous administration of tempol and pinacylboronate NPs [73]. Copyright 2018, American Chemical Society. (C) Protective effects of fullerene derivatives $Gd@C_{82}(OH)_{22}$, $C_{60}(OH)_{22}$, and $C_{60}(C(COOH)_2)_2$ against H_2O_2-induced damage in A549 and rBCECs cells [77]. Copyright 2009, Elsevier.

complications. In diabetes mellitus type 1 models, hyperglycemia damages the reproductive system, leading to testicular dysfunction and spermatogenic disruption. However, the application of fullerene can reduce ROS levels and reverse male sexual dysfunction and fertility impairment [80]. Another diabetes model has demonstrated that the ROS capture ability of fullerene leads to the amelioration of pancreas dysfunction and hepatic insulin resistance [81].

3.3. Redox reactive-oxygen-species-scavenging nanoparticles

3.3.1. Curcumin-based nanoparticles

Phenolic plant compounds are effective antioxidants in which the antioxidant property, capable of protecting plants from oxidative damage caused by ultraviolet radiation, results from the low O–H bond dissociation energies of the compounds. Curcumin, a plant polyphenol found in turmeric, can be used as an antioxidant and has anti-inflammatory, anticancer, and neuroprotective effects [82,83]. The neuroprotective function of curcumin NPs is manifested as a reduction in the oxidative stress occurring in neuronal cells [84]. Recently, Qian et al. prepared an injectable hydrogel loaded with curcumin for ROS scavenging in traumatic brain injury to ameliorate the regeneration and recovery of neurons [85]. Fernandes et al. developed an ideal stable material (curcumin-loaded liposomes) to cross the blood–brain barrier. Curcumin-loaded liposomes had antioxidant and anti-inflammatory

performance, which could effectively reduce oxidative stress induced by neuronal cells, suggesting the potential for neuroprotection [86]. Furthermore, the local injection of these NPs can lead to a significant decrease in ROS and RNS and protect ankle joints from LPS-induced inflammation (Fig. 8A) [87]. Recently, curcumin has been increasingly used in inhibiting oxidative stress and inflammation, in protecting cells in the central nervous system [87–89], and in treating chronic ulcers [90, 91] and I/R injury [92,93].

3.3.2. Bilirubin nanoparticles

Bilirubin (Bi), a natural metabolite that scavenges ROS and protects cells from oxidative stress, acts via an ROX-initiated redox reaction whereby water-insoluble Bi is oxidized to water-soluble biliverdin (Fig. 8B) [94]. Bi inhibits NOX-related ROS production and TLR4-mediated LPS inflammatory response by targeting the redox-sensitive transcription factor hypoxia inducible factor-1α (HIF-1α) [95]. Thus, Bi NPs exhibit potential for use as nanomedicines aimed at treating various inflammatory diseases [96], including ulcerative colitis [97,98], hepatic I/R injury [99], pulmonary fibrosis (PF) [100], AKI [101], and multiple sclerosis [102]. The latest eruption of COVID-19 had resulted in PF due to the acute respiratory distress syndrome (ARDS), and one of the key roles in ARDS was oxidative damage caused by local infiltration of immune cell. Keum et al. explored the therapeutic effect of the endogenous antioxidant and anti-inflammatory Bi on PF. The results
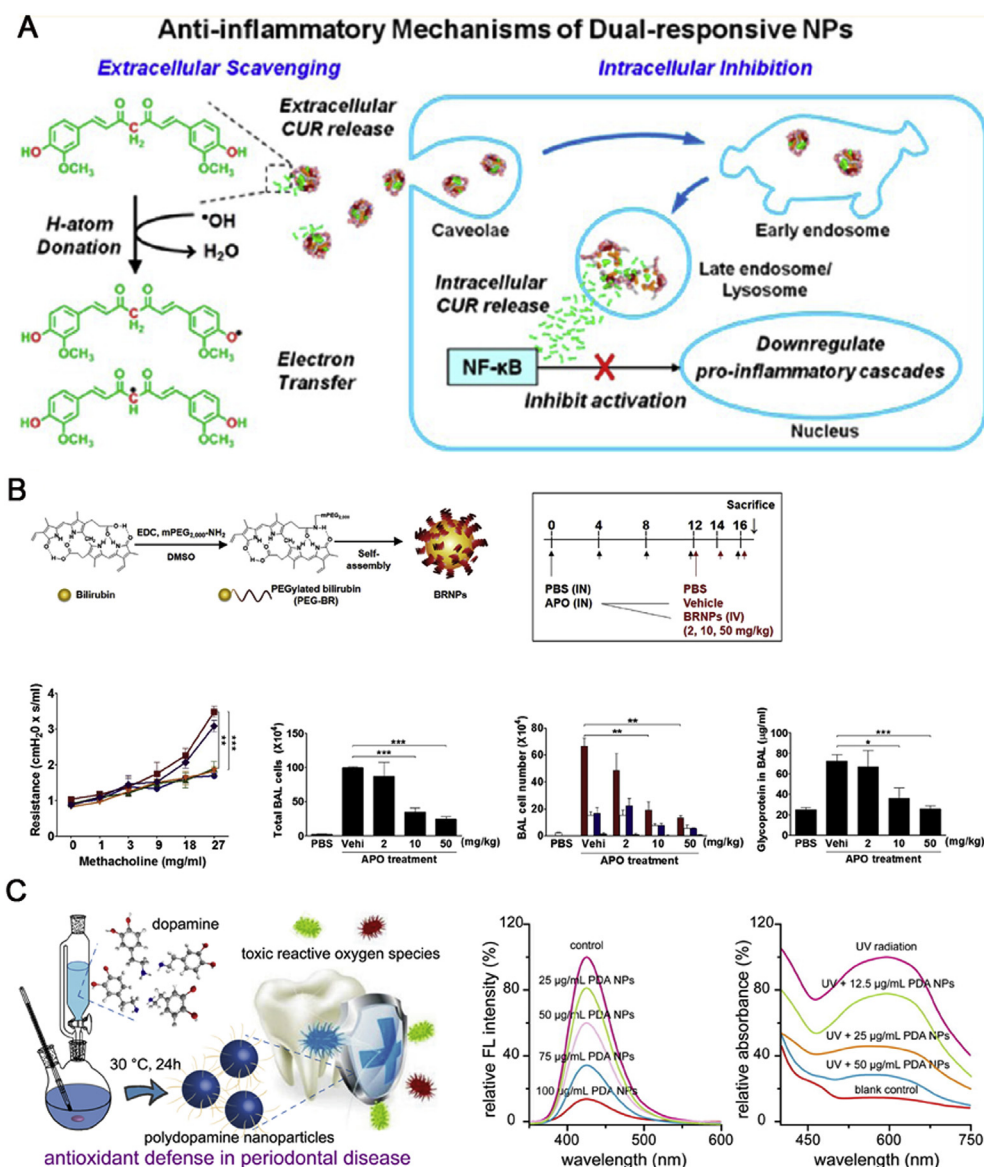
Fig. 8. (A) Schematics showing the composition/structure of dual-responsive bilirubin nanoparticles (Bi NPs) and their extracellular/intracellular anti-inflammatory mechanisms [87]. Copyright 2014, American Chemical Society. (B) Synthesis and effects of Bi NPs on murine experimental asthma [94]. Copyright 2017, Elsevier. (C) Schematic figure of the typical synthesis of polydopamine NPs as an efficient reactive oxygen species scavenger for periodontal disease, and their scavenging efficiencies of ·HO and $O_2\cdot^-$ [105]. Copyright 2018, American Chemical Society.

showed that Bi could preferentially accumulate in inflamed site, reduce oxidative stress, and effectively ease the symptoms in the PF mouse model [100]. In addition, Zhao et al. reported a ε-polylysine-Bi conjugate (PLL-BR) to embedding the islets to study its function on macrophage modulation activity during islet transplantation [103]. The PLL-BR was able to target and cluster to islets and exhibit excellent antioxidants and anti-inflammatory properties, and it was the first time to demonstrate that Bi and its derivatives could efficaciously accelerate the polarization of M2 macrophage and ameliorate the immune microenvironment to maintain functional islets. In summary, Bi offers a potential therapeutic strategy for inflammatory diseases due to its favorable antioxidant and anti-inflammatory properties.

3.3.3. Polydopamine nanoparticles

Polydopamine (PDA) as typical synthetic melanin has similar prominent antioxidation properties as melanin. Owing to the structural complexity of PDA, its exact antioxidant mechanism is still worth exploring. The free-radical scavenging mechanism of PDA may be related to the redox chemistry of the polycatechol structure, lifetime of inner radicals, and ultrafast energy transfer improved by ion binding [104]. The catechol can quench free radicals by providing hydrogen atoms on the phenolic hydroxyl group and decrease certain compounds by electron transfer, forming a steady quinone structure through the interaction between produced phenoxyl radicals and the second quenching free radicals [104]. PDA has excellent spectral ROS-scavenging ability, which has been widely exploited in oxidative stress–induced disease therapy. Bao et al. used biodegradable ROS scavenger PDA NPs to treatment oxidative-stress-induced periodontal disease (Fig. 8C) [105]. They inferred that the uptake transport-release performance of macrophages could be the metabolic avenue for PDA NPs in gums-macrophage, resulting in good biocompatibility [105]. In addition, PDA also has an excellent photothermal conversion effect. Recently, Battaglini et al. developed lipid-coated PDA NPs (L-PDNPs) that combine the antioxidant properties with photothermal effects for neurological disease treatment. L-PDNPs showed excellent ROS-scavenging ability in differentiated SH-SY5Y, prevented the mitochondrial dysfunctions caused by ROS, and stimulated the hyperplasia of neurites. This study provides a new strategy for using NIR-responsive antioxidant nanomaterials in neuronal studies [106]. Fu et al. designed several reduced PDA NPs to improve the antioxidative capacity of PDA NPs. The reduced PDA NPs, as an antioxidant, were loaded in hydrogel dressings to avoid the stimulation of external oxidative stress on cells for expedited wound healing [107].

In addition to NPs, various of nano structures have been reported to remove ROS, such as nanosheet [108–110], nanorod [111,112], nanotube [113,114], nanofiber [115,116], and nanomesoporous [117], have been reported to remove ROS. These nanostructures have many active sites, large specific surface areas, or a specific structural effect, thus improving their ROS-scavenging effect. For example, Lucente-Schultz et al. designed single-walled carbon nanotubes, which exhibited nearly 40 times greater ROS-scavenge ability than dendritic fullerene, which could be an attractive antioxidant for antioxidation [113]. Neacsu et al. reported a TiO_2-nanotube-modified flat Ti surface (Ti/TiO_2) to reduce immune responses and further explored the mechanism of the attenuated macrophage inflammatory activity using TiO_2 nanotopography. The signaling proteins of mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) pathways were the main regulation for the startup of the macrophage inflammatory process. The results show that TiO_2 nanotubes could reduce macrophage inflammatory reactions by inhibiting the MAPK and NF-κB pathways [114]. In addition, Wang et al. reported black phosphorus nanosheets (BPNSs) with flake-like DNA frameworks, which were beneficial to the kidney drug-targeting transmission for kidney therapy [108]. In an ROS-induced AKI mouse model, BPNSs, as an effective ROS scavenger, could target the kidney and ease cellular apoptosis caused by oxidative stress. Liu et al. developed a TiO nanobelt loaded with MoS (MoS@TiO) for antioxidation applications. Due to the multiple specific surface areas and active sites, MoS@TiO exhibited better dispersibility and catalytic activity. MoS@TiO could effectively eliminate the endogenous massive accumulation of ROS to normal levels in an oxidative stress mouse model [118].

4. Conclusions and future perspective

For the safe and effective treatment of diseases related to oxidative stress, the application of antioxidant nanotechnology is rapidly becoming a viable therapeutic strategy and exhibits significant promise. However, its clinical transition is subject to multiple challenges.

For maximizing therapeutic and targeting efficacy, nanomaterials targeting the release of antioxidants and spatiotemporal control of their activities exhibit considerable promise. Ultrasmall ROS-scavenging nanomaterials modified with targeting molecules can reduce the rate of mitochondrial ROS production plants. Furthermore, nanomaterials can rapidly pass through multiple complex physiological and biological barriers associated with (for example) the isolation of the mononuclear phagocytic system and the restriction of hemorheology and vascular flow, non-specific distribution, cell internalization, and endoplasmic/lysosome escape. Methods for increasing the half-life of antioxidants and their accumulation at damaged sites have been extensively investigated. However, only a few antioxidant nanomaterials have been able to completely address these issues. Aiming at this, our overall direction is to enhance the targeting efficiency of antioxidant nanomedicines by all means, for example, screening the best particle size, which has the strongest antioxidative ability, coupling targeting substance on the surface of nanomaterials. Currently, there is a need to establish a complete screening and evaluation system for antioxidant nanomedicines.

The 'redox pathology' induced by immoderate antioxidation is not clarified. It is known that low levels of ROS/RNS are necessary for life activities. They play a part in several biochemistry processes, such as signal transduction and metabolic and inflammatory regulation. Therefore, there is an urgent need for dynamic monitoring of ROS/RNS levels in organisms. In addition, precise research on the profile of ROS/RNS-related biochemistry processes remedy the fear of breaking the redox balance.

Furthermore, because of quantum size effects and their large surface area-to-volume ratios, the properties of nanomaterials are unique. For small particles, such properties are observed and may be attributed to multiple nano-biological interactions leading to toxic effects. Furthermore, clinical translation requires the additional study of long-term toxicities, degradation mechanisms, metabolism, and scavenging pathways of nanomaterials. To solve these problems, recent application of bioinspired polymer nanomaterials with innate biocompatibility and biodegradability is expected. Multiple preclinical studies demonstrated that the use of antioxidant nanomaterials leads to no obvious adverse reactions [149]. Future studies should focus on characteristics that dramatically affect the biocompatibility of nanomaterials, including particle size, composition, concentration, and environmental conditions (such as redox conditions and pH).

The specific activity and stability details of such nanomaterials in vivo remain unclear and reports on stable NPs with ROS- and RNS-removal capabilities are rare, despite the ongoing research and advances in materials science and nanotechnology. Furthermore, the development of simple processes for the large-scale production of high-efficiency antioxidant nanomaterials plays an important role in clinical transformation. Antioxidant nanomaterials require multiple complex or laborious synthesis processes, and their potential for clinical transformation is typically limited by problems associated with large-scale pharmaceutical production. Directing at these issues, subsequent studies should attach importance to simplified synthesis of antioxidant nanomaterials, which makes it easy to quantity production. Moreover, computer modeling is available for predicting ROS-/RNS-scavenging nanomedicines' interactions, so as to determine their stability.

To summarize, nanomedicine is rapidly developing, and the basic understanding of antioxidant nanomaterials has significantly increased. In future, the challenges associated with these materials will be addressed. Future investigations will be aimed at achieving the widespread application of antioxidant nanomedicine for preventing and/or treating inflammatory conditions.

Declaration of competing interest

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

Acknowledgments

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