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Nanozymes for Treating Ocular Diseases

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Nanozymes, characterized by their nanoscale size and enzyme-like catalytic activities, exhibit diverse therapeutic potentials, including anti-oxidative, anti-inflammatory, anti-microbial, and anti-angiogenic effects. These properties make them highly valuable in nanomedicine, particularly ocular therapy, bypassing the need for systemic delivery. Nanozymes show significant promise in tackling multi-factored ocular diseases, particularly those influenced by oxidation and inflammation, like dry eye disease, and age-related macular degeneration. Their small size, coupled with their ease of modification and integration into soft materials, facilitates the effective penetration of ocular barriers, thereby enabling targeted or prolonged therapy within the eye. This review is dedicated to exploring ocular diseases that are intricately linked to oxidation and inflammation, shedding light on the role of nanozymes in managing these conditions. Additionally, recent studies elucidating advanced applications of nanozymes in ocular therapeutics, along with their integration with soft materials for disease management, are discussed. Finally, this review outlines directions for future investigations aimed at bridging the gap between nanozyme research and clinical applications.

1. Introduction

Nanozymes are nanomaterials endowed with enzyme-like catalytic activities, capable of converting enzyme substrates into products.[1] The name of nanozymes was first introduced in 2004 by Scrimin et al.,[2] who demonstrated the ribonuclease-like behavior of gold nanoparticles (NPs) functionalized with triazacyclonane, allowing for the cleavage of phosphate esters. Subsequently, in 2007, magnetic iron oxide NPs (Fe_3O_4) emerged as the first nanozyme of significant general interest due to their peroxidase-mimicking action, facilitating their utilization in immunoassays and therapeutic interventions.[3] Since then, a diverse range of nanomaterials exhibiting catalytic properties has been identified, each with varying underlying mechanisms. Recent investigations have revealed the catalytic activities of various metal and metal oxide NPs (such as iron oxide, nanoceria, and gold NPs), carbon-based nanomaterials (including graphene oxide and carbon dots and nanotubes), and numerous metal-organic frameworks (MOFs), replacing natural enzymes for applications.[1c,4] Notably, iron oxide, nanoceria, or cerium oxide NPs have emerged as highly promising nanozymes, exhibiting multi-enzyme-like activities encompassing oxidase (OXD), glucose oxidase (GOD), peroxidase (POD), catalase (CAT), and superoxide dismutase (SOD).[1a,c,4,5]

Compared to enzymes, nanozymes offer several advantages, including simple and cost-effective synthesis, high stability in harsh conditions (such as temperature and pH), ease of surface modification and functionalization, and multi-functional catalytic activities.[6] Due to these properties, their multi-catalytic activities, and the use of biologically relevant substrates, nanozymes have been investigated for the treatment of diseases associated with excessive ROS, including cancer, Alzheimer's disease, Parkinson's disease,[7] acute kidney injury,[8] and ischemic stroke.[9] However, their clinical translation still encounters challenges.[6a,b,10] Similar to other inorganic nanomaterials utilized for drug delivery and therapy, safety and toxicity are major concerns of nanozymes, especially when administered systemically.[6b,11]

With emerging studies on nanozyme development, we believe that ocular diseases can provide a unique opportunity to showcase the therapeutic potential of nanozymes. Eyes are uniquely exposed to the external environment, characterized by intricate anatomical and physiological barriers including the blood-retina barrier, corneal barrier, and blinking, which present significant hurdles for effective drug delivery to disease sites in eyes. This limitation often leads to diminished bioavailability of current

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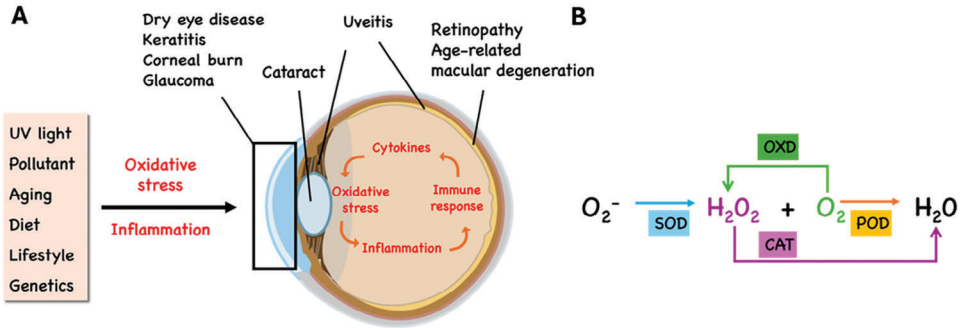

Figure 1. Potential applications of nanozymes in ocular diseases. A) Common ocular diseases are linked to oxidative stress and inflammation. B) Redox reactions scavenging ROS mediated by various nanozymes.

therapeutic agents and requires frequent administration.[12] Typically, a high dosage of drugs is necessary to adequately deliver medication to the eye, potentially resulting in irritation, burning, or redness of the eye surface.[12] Nevertheless, research in nanomaterials has exhibited promise in surmounting the blood-retina barrier owing to their nano-scale dimensions (less than 100 nm) and adjustable physicochemical properties for drug delivery.[13] This enhancement contributes to improving the efficacy, bioavailability, safety, and stability of ocular drug delivery.[14] Since eyes are exposed, nanozyme-based therapeutic agents can be directly applied, bypassing the need for systemic delivery.

Nanozymes demonstrate stability and high light-scattering capabilities, making them suitable for enhancing the monitoring and diagnosis of eye diseases. They are also effective for detecting nanozymes delivery using optical coherence tomography (OCT).[15] Additionally, ocular diseases often involve multifactored or overlapping mechanisms.[16] Nanozymes have the potential to target multiple disease pathways simultaneously, thereby improving therapeutic efficacy.[6a,17] Furthermore, beyond their primary role as therapeutic agents, nanozymes can be used to deliver small molecules and integrated with soft biomaterials such as contact lenses (CCLs)[18] or microneedles,[19] which have already demonstrated efficacy in conditions such as keratitis.[20] These combined approaches provide an interesting platform for leveraging the unique properties of nanozymes in the treatment of various ocular diseases.

Several review papers have been published specifically addressing the utilization of nanoceria in the context of retinal diseases[21] or in ocular disease in general.[22] This year, a review paper briefly summarized the use of nano-antioxidants in eye without touching upon nanozymes.[23] Two studies explored graphene quantum dots in the context of eye diseases, although these studies did not investigate the enzymatic-like effects of graphene quantum dots.[24] The present review aims to discuss the latest research on the application of various metal-based nanozymes to different ocular diseases. It starts with elucidating the mechanisms or pathologies of ocular diseases, followed by exploring the enzymatic aspects of nanozymes. Moreover, this review evaluates both independent applications of nanozymes in ocular therapeutics and their integration with soft materials in ocular disease management.

2. Ocular Diseases, a Special Opportunity for Nanozymes

In **Figure 1A**, various eye disease locations are illustrated. The eye can be categorized into the anterior and posterior segments, each with distinct structures and functions. The anterior segment comprises the tear film, cornea, conjunctiva, iris, ciliary body, lens, and aqueous humor, while the posterior segment includes the sclera, choroid, retina, Bruch's membrane, vitreous humor, optic nerve, and retinal blood vessels.[25] This division is not only anatomical but also relevant to therapeutic challenges. Topical administration is commonly used for treating anterior segment disorders but is often ineffective for posterior segment disorders due to ocular barriers. Injection into the posterior chamber is a more effective but invasive treatment for posterior diseases.[26] Despite anatomical and therapeutic differences between the anterior and posterior segments, ocular diseases in both segments often have similar pathologies or disease mechanisms.

Many ocular conditions, such as dry eye diseases (DED), age-related macular degeneration (AMD), and glaucoma, exhibit multi-factored etiologies that remain incompletely understood.[16] Nonetheless, they frequently feature elevated levels of oxidative stress, inflammation, and mitochondrial dysfunction factors, which nanozymes can potentially mitigate. Oxidation and inflammation affect both the anterior (e.g., DED, keratoconus, cataracts) and posterior (e.g., AMD, diabetic retinopathy, glaucoma) segments of the eye.[27]

Maintaining an equilibrium between the synthesis and neutralization of reactive oxygen species (ROS) is pivotal for cellular homeostasis, immune responses, and visual function.[27a] The mitochondrial electron transport chain for energy generation emerges as the prominent ROS source.[28] When the ROS balance is disrupted, oxygen can undergo partial reduction, yielding free radicals, like superoxide ($O_2\bullet^-$) and hydroxyl radicals ($\bullet OH$).[28] Excessive ROS production can damage DNA, proteins, lipids, and metabolites, thereby disrupting cellular integrity. The ROS elimination system includes endogenous anti-oxidative enzymes such as POD, CAT, and SOD (Figure 1B).[27b,28] Oxidative stress is acknowledged as an initial trigger in the inflammatory cascade.[29] For example, when oxidative stress occurs by increased OXD activities, the enzymatic activity diminishes. Initially, CAT activity decreases, followed by a decline in SOD

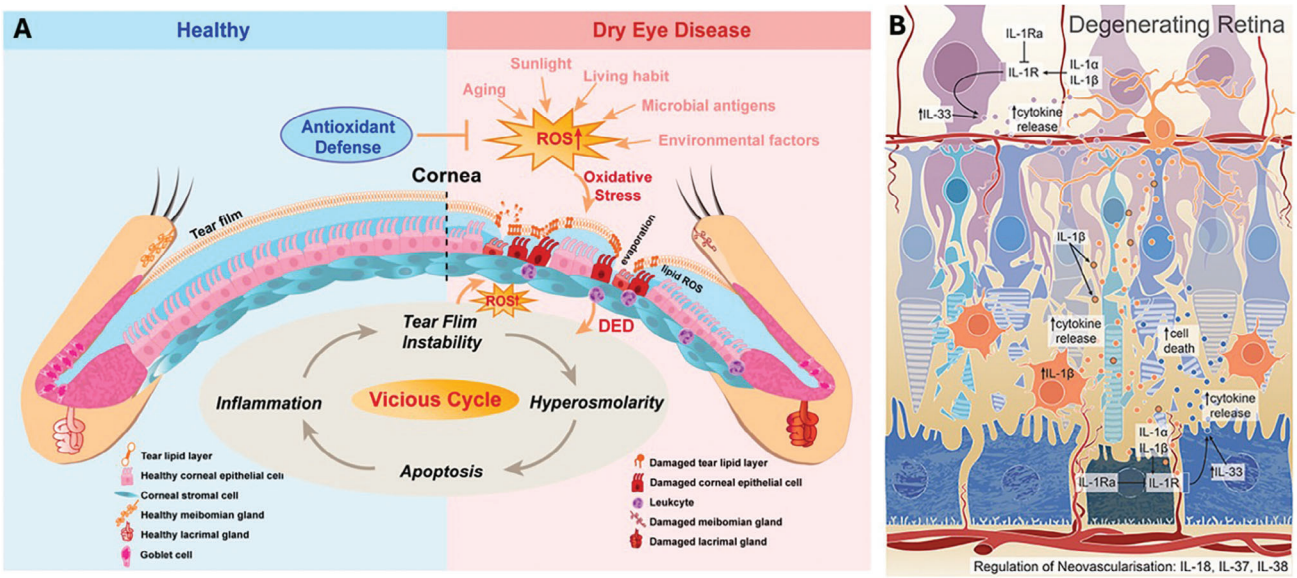

Figure 2. Oxidation and inflammation in eye diseases. A) The vicious cycle of DED is driven by oxidation and inflammation. Adapted with permission.[51] Copyright 2023, Multidisciplinary Digital Publishing Institute. B) Cytokine production in degenerating PRs leads to cell death, inflammation, and angiogenesis. Adapted with permission.[52] Copyright 2019, Frontiers Media SA.

activity. This succession results in the buildup of $O_2\bullet^-$ and •OH, causing further harm to the cornea and triggering immune responses and inflammation.[30] It highlighted the intricate interplay between these two phenomena. This section illustrates the collective influence of oxidation and inflammation on the progression of various ocular diseases.

2.1. Oxidation and Inflammation in the Anterior Segment

Dry eye disease: According to the Tear Film and Ocular Surface Society Dry Eye Workshop II report, DED is characterized as a complex ailment affecting tears and the ocular surface, potentially leading to discomfort, visual disturbances, unstable tear film, and ocular damage. It is often associated with an elevated tear film osmolarity and corneal inflammation.[31] DED is a prevalent condition worldwide, with a prevalence ranging from 5% to 50%.[31] The primary treatments for DED typically involve tear supplementation, applying heat to soften the secretary substance that blocks tear glands, avoiding external triggers, and discontinuing medications that contribute to DED.[32] While inflammation, regulated by the pyrin domain-containing 3 (NLRP3) inflammasome, is a central component of the vicious cycle in DED, ROS also plays a critical role by modulating inflammation and immune responses upstream (**Figure 2A**).[29b,33] Therefore, conventional eye drop prescription targeting inflammation alone may not provide optimal treatment for DED, not to mention the ocular barriers that reduce its bioavailability.[32a]

Keratitis or corneal burn: The two most prevalent ocular infections are conjunctivitis and keratitis, with microbial keratitis alone affecting up to 2 million individuals annually worldwide, with a higher concentration in South East and East Asia.[34] While bacterial infections, primarily gram-positive bacteria, constitute the majority of cases, keratitis can also be caused by yeast-like fungi, filamentous fungi, acanthamoeba, and viruses.[34] Major risk factors for ocular infections include ocular ulcers, infected CCLs, and pre-existing ocular diseases like DED.[35] Clinical management typically involves topical or intracorneal administration of antibiotics, but due to the barriers on eyes, the bioavailability of topical antibiotics is limited to 5%.[36] Infectious keratitis is usually associated with inflammation characterized by the infiltration of immune cells, elevated ROS level, and the accumulation of pro-inflammatory cytokines,[37] as well as lipid mediators such as prostaglandin and leukotrienes.[38]

2.2. Oxidation and Inflammation in the Posterior Segment

The retina is recognized as one of the tissues with the highest energy needs, primarily driven by the metabolic demands of photoreceptors (PRs).[39] Within the retina, rod and cone PRs have elevated oxidative metabolic rates, particularly due to exposure to a significant oxygen gradient. This gradient is highest in the choroid and sharply decreases in the outer retina, which lacks a direct blood supply.[39,40] PRs are consistently exposed to light, which can trigger the phototoxicity associated with oxidative stress. Additionally, the release of pro-inflammatory cytokines (Figure 2B), such as interleukin (IL)−1β and tumor necrosis factor-alpha (TNF-α), triggers retinal vascular permeability and cell apoptosis by activating the NLRP3 inflammasome in the retina. These eventually would lead to the risk of AMD, diabetic retinopathy, and macular edema.[41]

Age-related macular degeneration: AMD is a prevalent disease that influences the central zone of the retina, known as the macula, which is crucial for high-quality vision.[42] It is one of the reasons for blindness in the elderly and presents in two main stages: dry AMD, characterized by the accumulation of lipofuscin and drusen, leading to central vision blurring.[43] On the other hand,

wet AMD is more severe, involving abnormal blood vessel growth beneath the macula, resulting in fluid leakage, PRs degeneration, visual distortion, and permanent vision loss if left untreated.[44] Despite its high prevalence, the therapeutic options for AMD remain limited. Current treatments often involve injections of vascular endothelial growth factor (VEGF) antibodies in the vitreous humor, which can lead to complications such as infection, retinal detachment, or intraocular hemorrhage.[41b,45] NPs have been explored as potential treatments for AMD, but their limited antioxidative efficacy, safety concerns, and challenges related to delivery routes have restricted their progress to the preclinical stage of research.[46]

Uveitis: Uveitis is a group of conditions characterized by inflammation of the uvea, which can affect the iris, ciliary body, and choroid, or extend to the retina in the posterior segment.[47] Various factors, including autoimmune disorders, infections, and environmental triggers, can contribute to the development of uveitis, with oxidative stress playing a pivotal role in its progression.[48] Elevated levels of ROS during uveitis activate redox signaling pathways and transcription factors such as NF-κB, leading to the production of inflammatory mediators including cytokines, chemokines, and enzymes such as iNOS and COX-2.[49] Common therapeutic approaches to uveitis involve the use of alkylating agents, corticosteroids, and antimetabolites. However, these treatments often entail nonspecific and systemic adverse effects.[50]

Collectively, oxidation and inflammation represent the fundamental disease pathways in the majority of ocular diseases. Hence, balancing the ROS levels on the ocular surface has emerged as a promising strategy. It is worth noting that conditions such as glaucoma, cataracts, and retinopathy are also influenced by oxidative stress. However, these specific diseases will not be addressed in this section.

3. Types of Nanozymes for Treating Ocular Diseases

The ROS-scavenging capability of nanozymes primarily arises from their redox activities. Metal-based nanozymes, such as metals or metal oxides, possess a reactive metallic center capable of undergoing oxidation to facilitate ROS scavenging by releasing an electron to ROS and bonding with an oxygen atom. The effectiveness of ROS scavenging depends on several factors, including the oxidation states of the metal center, temperature, pH, and the presence of a reduction agent in the reaction.[5,6c,53] In this section, we highlight a few types of metal-based nanozymes that have been employed in recent research for the treatment of ocular diseases.

3.1. Cerium (Ce)-Based Nanozymes

Since 2006, cerium oxide, also known as nanoceria, has been recognized as an antioxidant capable of protecting neuronal cells by reducing ROS levels.[54] Nanoceria can be considered to be comprised of a mixture of Ce_2O_3 and CeO_2. When $O_2\bullet^-$ interacts with Ce_2O_3, an electron from Ce^{3+} in the 4*f* subshell is transferred to oxygen, yielding H_2O_2, mimicking SOD activity. During this process, Ce^{3+} undergoes oxidation to Ce^{4+} (an oxidation of 4), subsequently reacting with H_2O_2 to generate H_2O and O_2 upon acquiring an electron, thereby emulating CAT action.[5,22] This chain reaction demonstrates the ability of cerium atoms to undergo valence conversion, serving as an example of multi-substrate nanozymes for inherent anti-oxidative, anti-inflammatory, and anti-angiogenic effects.[5]

Nanoceria is also the most studied nanozymes for eye diseases.[22] It has demonstrated protective effects on human retinal pigment epithelium-19 (ARPE-19) cells[55] and human lens epithelial cells (HLECs)[56] from oxidative stress, alleviated the progression of diabetic cataracts,[57] and suppressed oxidative stress in DED.[58] Additionally, the hollow structure of nanoceria enables a high drug-loading efficiency,[59] potentially facilitating the delivery of ophthalmic drugs. However, concerns regarding the potential toxicity of nanoceria have arisen, particularly when applied to the eye. Although their small size facilitates delivery to the retina, nanoceria demonstrated extended retention times in circulation, lasting up to 6 months after intravenous administration or over 1 year following a single intravitreal injection.[60] Prolonged exposure to nanoceria has been linked to cellular mitochondrial metabolic dysfunction and cytotoxicity, accompanied by localized inflammation in the spleen and liver, which are the primary organs responsible for nanoceria clearance.[61] Hence, optimization of the size, surface modification, and administration routes could be explored to mitigate potential side effects and regulate nanoceria clearance.

3.2. Iron (Fe)-Based Nanozymes

Prussian blue (PB), composed of ferrous ferrocyanide salts, functions as an iron-containing nanozyme characterized by N-coordinated Fe ions (FeN_x, where x ranges from 2–6), reflecting the diverse valency states of Fe atoms.[5] PB's structure consists of a 3D network containing Fe^{3+} and Fe^{2+} ions coordinated with CN^- ligands. The charge transfer between Fe^{3+} and Fe^{2+} in the 3*d* subshell confers PB with multi-enzyme activities, including CAT and SOD-like functions. These properties have shown therapeutic potential in addressing ROS-induced cell damage and treating various diseases such as liver inflammation, pancreatitis, wound healing, and stroke.[9a,62] In ocular applications, PB demonstrates efficacy in reducing ROS levels associated with retinal diseases like AMD.[62] Moreover, leveraging PB's color diversity by coordinating with different precursors, Liu et al.[62] created other PB analogs such as Prussian white, Berlin green, and Prussian yellow as ROS-scavenger and coloring materials in cosmetic CCLs.

Iron oxide has been extensively researched to have enzyme-like activity, primarily due to the multiple valency of Fe ions and its Fenton action, producing highly toxic •OH for tumor suppression.[63] In addition to iron oxide, Fe-based nanozymes can also be synthesized using MOFs. Jiang et al.[64] demonstrated this by coordinating Fe ions with curcumin, a natural anti-oxidative polyphenol molecule, to increase the bioavailability of curcumin in eye. Their approach involved Fe^{3+} coordination with the phenol groups of curcumin, transforming it into a black Fe-curcumin solution with enhanced water solubility. This strategy exhibits anti-inflammatory and anti-oxidative effects attributed to

both Fe ions and curcumin, offering potential synergistic benefits in treating uveitis.

3.3. Manganese (Mn)-Based Nanozymes

The enzyme-like action of Mn-based nanozymes was demonstrated by Liu et al. in 2012.[65] MnO_x has multiple valency states of 2 to 4, excellent degradability, and cost-effectiveness, especially manganese oxides like MnO_2, MnO, Mn_2O_3, Mn_3O_4, and MnO_x.[65] In comparison to ceria, MnO_2 was found to exhibit more potent effectiveness in neutralizing ROS due to its more valence states and larger surface area, facilitating substrate reactions.[66] Mn-based nanozymes emulate various enzyme activities such as SOD, POD, and OXD, offering the potential for inhibiting tumor growth.[5] Moreover, the Mn^{2+} ions produced during redox reactions serve as diagnostic tools for clinical imaging.[67] A recent study indicated their anti-oxidative and anti-apoptotic effects in treating DED, attributed to their SOD activity.

3.3.1. Platinum (Pt)-Based Nanoparticles

Pt-based nanozymes are currently sold in Japan as dietary supplements and facial products.[68] These nanozymes, which exhibit oxidation states of 2 to 4, possess inherent multi-enzymatic capabilities, imitating the roles of POD, CAT, and SOD.[68,69] Similar to other types of NPs, PtNPs tend to develop a protein corona when exposed to bodily fluids such as serum. This protein layer can potentially reduce the catalytic functions of the PtNPs outside cells.[70] Nevertheless, the uptake of PtNPs into cells and the accumulation of lysosomes may lead to the release of NPs. This occurs due to the degradation of the protein corona in the proteolytic environment and the acidic pH commonly observed in tumor regions or highly metabolically active cells, although we believe that a full release of the corona is difficult since new proteins may be further adsorbed. Last year, the application of PtNPs has been studied in ocular disease, tackling ROS-induced retinal disease.[71]

3.4. Dual-Metal Nanozymes

The aforementioned nanozymes contain a single type of metal. Despite their success in numerous studies, they still face uncertainty and challenges. First, their heterogeneous nanostructures result in diverse compositions, leading to challenges such as limited selectivity and ambiguous catalytic sites.[72] Additionally, it remains difficult to precisely control their structure, often resulting in insufficient metal utilization and restricted enzyme-like activities.[73] To address these limitations, researchers developed dual-metal nanozymes in 2014.[74] These dual-metal nanozymes provide more accessible active sites and hold promise in overcoming the limitations associated with single-metal reactions.[75] Last year, dual-metal Fe and Mn were integrated onto the surface of N-doped carbon materials with a pointed dodecahedral structure. The dual-atom nanozymes of Fe and Mn form more accessible active sites which effectively neutralize excess ROS on the ocular surface.[76]

4. Application of Nanozymes in Ocular Diseases

Increasing attention has been directed toward using nanozymes for the treatment of ocular diseases. Recent developments in nanozyme technology have focused on the incorporation of different polymers, small molecules, or soft materials for ocular applications. In this section, we highlight recent studies on nanozyme applications, including metal coordination-driven nanozyme, nanozyme as drug delivery carriers, integration with other nanoparticles, and incorporation into soft materials for both anterior and posterior diseases (**Table 1**).

4.1. Nanozyme Application of Anterior Eye Diseases

4.1.1. Metal Coordination-Driven Nanozyme

MOFs, often crafted to emulate the redox reactions facilitated by redox enzymes, generally exhibit lower catalytic capabilities compared to their natural metalloenzymes.[77] To improve the catalytic efficiency of MOFs, a common strategy includes modifying the linker substituents within MOFs, which adjusts the electronic configuration of the metal and modifies their enzymatic-like functions. Additionally, incorporating surface-modified halogen atoms may enhance the activity of nanozymes.[86] Tang et al.[77] investigated the efficacy of 2D halogen-coordinated copper nodes in treating corneal burns. The authors synthesized various Cu-X MOFs (with X being Cl, Br, or I) by combining copper ions with halogen ions and 4,4′-bipyridine (**Figure 3A–C**). Among these, Cu-Cl MOF exhibited the most efficient electron transfer and ROS activity, potentially due to the largest dihedral angles between the copper atomic planes and the 4,4′-bipyridyl planes and different bonding abilities (Figure 3D,E). These MOFs showed no cytotoxicity to human corneal endothelial cells (HCECs) and effectively reduced intracellular ROS levels in H_2O_2-treated cells through nuclear factor-erythroid factor 2-related factor 2 and mitogen-activated protein kinase pathways (MAPK, Figure 3F). In both alkali burn and H_2O_2 animal models, topical administration of Cu-Cl three times daily for 10 days reduced corneal inflammation and promoted corneal healing. Further studies are needed to assess the systemic toxicity and compare their effects with other treatments.

The MOF-based nanozymes mentioned above are ≈100 nm in size. Smaller NPs are more favorable for delivery to the eye as they can better penetrate tight cell layers and barriers. In 2024, Chen et al. engineered ultrasmall Ce-MOFs (2 nm) for managing DED.[78] By modifying the concentrations of the raw materials, cerium nitrate, and terephthalic acid, the authors synthesized three Ce-MOFs with sizes of 213, 36, and 2 nm, respectively. Among these, the 2 nm Ce-MOFs exhibited the most potent effect on ocular penetration and reduced H_2O_2-induced oxidative stress in vitro through a SOD-like action in HCECs. In addition, it effectively suppressed cell death. In vivo experiments using a DED mouse model showed that after a 13-days topical treatment with CE-MOFs, the 2 nm formulation promoted tear stability and maintained corneal integrity without causing side effects or irritation in the eye. This study further supports the notion that ultra-small nanozymes possess superior therapeutic effects, antioxidant capacity, and ocular penetration capabilities.

Table 1. Recent studies of nanozyme applications in ocular diseases.

	Design	Nanozymes	Ocular diseases	Routes	Mechanisms	Clinical significance	Reference
Anterior	**(1) Metal coordination driven nanozyme**						
	Halogen-coordinated copper nodes	Cu-X, X = halogen	Corneal burns	Topical eye drops	Anti-oxidation Anti-apoptosis	• Scavenging ROS • Regulating the NRF2 and MAPK pathways	[77]
	Ultra-small Ce-MOFs	Nanoceria	DED	Topical eye drops	Anti-oxidation Anti-apoptosis	• Scavenging ROS • Increasing ocular penetration	[78]
	(2) Nanozyme as a drug delivery carrier						
	Gabapentin-loaded nanoceria	Nanoceria	DED	Topical eye drops	Anti-oxidation, Anti-inflammation Anti-apoptosis Anti-angiogensis	• Prolonging retention time, • Controlling drug release • Scavenging ROS • Suppressing inflammatory mediators	[79]
	Tannin-coordinated nanozyme hydrogels	Cobalt tetroxide	Keratitis	Topical eye drops	Anti-oxidation Anti-apoptosis Anti-bacteria	• Broad-spectrum anti-microbial • Scavenging ROS in HCECs and fibroblasts HCFs • Suppressing inflammatory factor expression	[80]
	(3) Integrating nanozyme with polymeric materials or nanomaterials						
	PEGylated nanoceria	Nanoceria	DED	Topical eye drops	Anti-oxidation Anti-inflammation	• Scavenging ROS Maintaining corneal integrity • Increasing goblet cell numbers in the conjunctiva	[81]
	Dual-atom nanocrystals	Iron oxide and manganese oxide	DED	Topical eye drops	Anti-oxidation Anti-inflammation	• Scavenging ROS • Inhibiting NLRP3 • Suppressing cell apoptosis	[76]
	(4) Integrating nanozyme with soft materials						
	NIR-photothermal nanozymes	Iron oxide	Keratitis	Microneedle on eye	Anti-oxidation Anti-inflammation Anti-bacteria	• Increasing oxidative hydroxyl in bacteria • Reducing inflammatory markers	[20]

(*Continued*)

Table 1. (Continued)

	Design	Nanozymes	Ocular diseases	Routes	Mechanisms	Clinical significance	Reference
Nanozyme-CCLs	Prussian blue and its analogs	Corneal surface disease	CCLs on eye	Anti-oxidation Anti-inflammation	• Scavenging ROS • Suppression of inflammation • Restoration of corneal thickness		[62]
Manganese oxide – graphdiyne microneedle	Manganese oxide	Keratitis	Microneedle on eye	Anti-oxidation Anti-inflammation	• Enhanced bioavailability • Relieving ocular hypoxia • Promoting the healing of corneal epithelial damage.		[82]
Posterior	**(1) Nanozyme as a drug delivery carrier**						
	Fe-curcumin nanozymes	Iron oxide	Uveitis	Oral route with single IV injection	Anti-oxidation Anti-inflammation	• Decreasing levels of inflammatory markers in both eye and serum	[64]
	Fe-quercetin polymer nanodots	Iron oxide	Diabetic retinopathy	Oral route	Anti-oxidation Anti-inflammation	• Scavenging ROS • Prolonged resident time • Regulating the NF-κB, TNF and PI3K/Akt/mTOR pathways	[83]
	(2) Integrating nanozyme with biomimetic materials or nanomaterials						
	Cerawafer	Nanoceria	AMD	Patch on eye	Anti-oxidation Anti-inflammation	• Scavenging ROS Downregulating VEGF in the retina	[84]
	Mitochondrial-targeting PtNPs liposome	Platinum oxide	Retinopathy	IV injection	Anti-oxidation Anti-inflammation Anti-	• Reducing mitochondrial oxidative damage • Normalizing neovascularization	[85]
	Platinum NPs coated with RSA	Platinum oxide	AMD	IV injection	Anti-oxidation Anti-inflammation	• Reducing photo-oxidative damage • Maintaining the functionality of RPs and retinal ganglion cells	[71]

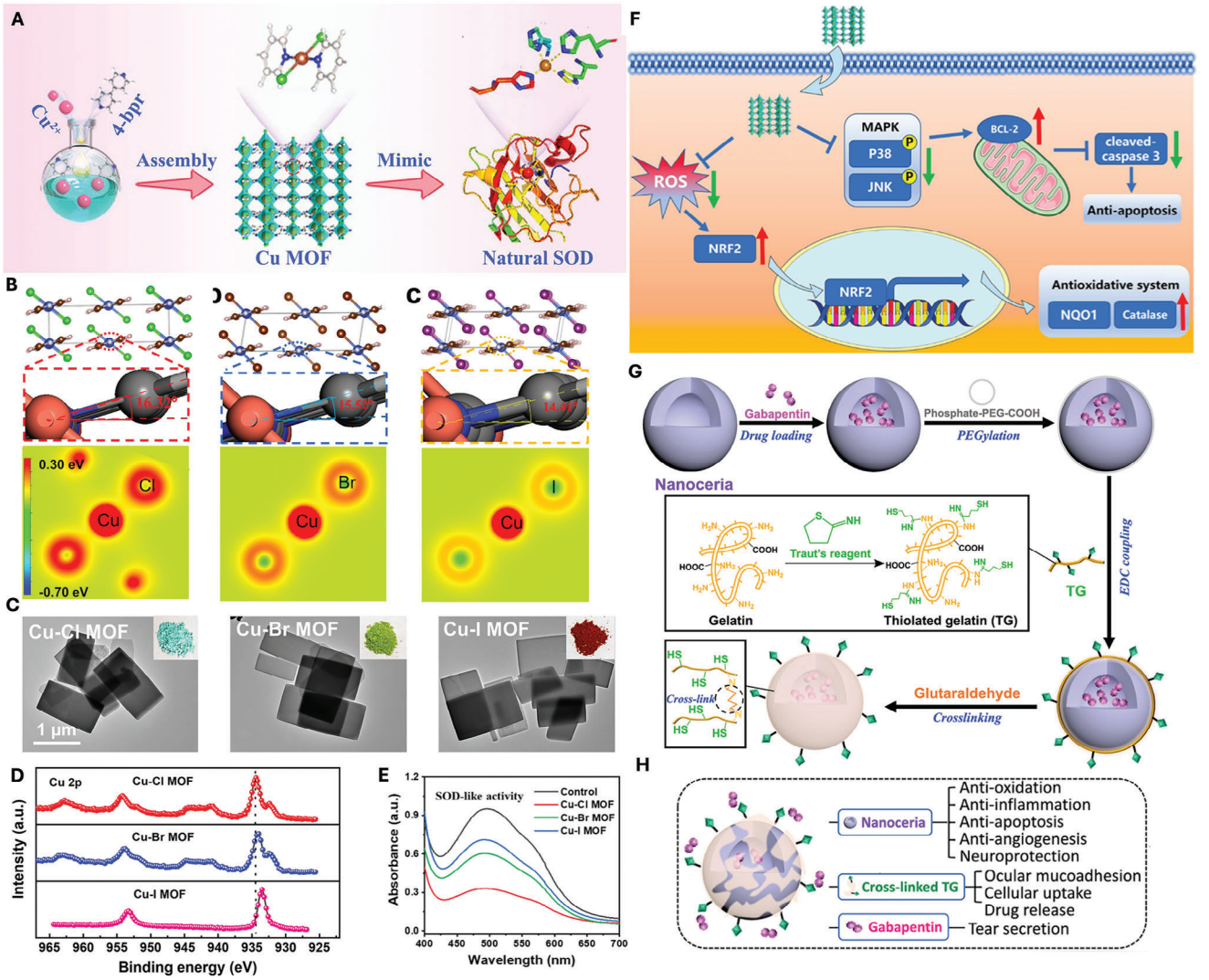

Figure 3. Nanozymes for treating corneal diseases. A) Schematic diagram illustrating the synthesis of the Cu-X-MOF nanozymes. B) Visual representation showing the angle between the copper atoms and the 4,4′-bipyridyl plane in various Cu-X MOFs, along with a diagram of the 2D Bader charge distribution. C) Transmission electron microscopy (TEM) images of Cu-X MOFs. D) XPS spectra of the Cu-X MOFs, showing the electronic configurations of Cl 2*p*, Br 3*d*, I 3*d*, and Cu 2*p*. E) Spectral analysis of SOD-activities using Cu-X MOFs. F) Schematic diagram showing the mechanisms through which the Cu-Cl MOF mitigates oxidative stress and apoptosis. Adapted with permission.[77] Copyright 2023, Springer. G) Schematic diagram showing the synthesis of gabapentin-loaded, cross-linked, and thiolated gelatin-modified nanoceria. H) Overview of the biological and pharmacological activities of DED. Adapted with permission.[79] Copyright 2023,American Chemical Society.

4.1.2. Nanozymes as a Drug Delivery Carrier

While previous studies on nanoceria in ocular disease have utilized bare nanozymes and administered them intravitreally,[22] recent studies have delivered nanoceria to the eye by incorporating it as a drug delivery carrier. Last year, Yang et al.[79] developed a formulation called gabapentin (Gab)-loaded, cross-linked, thiolated gelatin-modified nanoceria (G/Ce-XL) to improve the therapeutic potential of nanoceria for managing DED (Figure 3G). This formulation integrates gabapentin, an off-label analgesic, to alleviate ocular pain associated with aqueous-deficient DED, while nanoceria serves as multi-functional nanozymes with antioxidative, anti-inflammatory, anti-apoptotic, and anti-angiogenic properties. G/Ce-XL was synthesized by conjugation with crosslinked thiolated gelatin using EDC coupling. This formulation enhanced mucosal adhesion, prolonged retention time, improved cellular uptake, and allowed controlled drug release in response to gelatinase in the tear film (Figure 3H). In vitro assays demonstrated potent anti-oxidative activity of Gab-nanoceria, scavenging ROS and suppressing the production of inflammatory mediators (prostaglandin and VEGF). In a DED rabbit model, G/Ce-XL treatment increased tear production, reduced corneal staining, and improved tear breakup time. Moreover, the drug release rate from Ce-XL was affected by the crosslinking density, with slow and sustained medication release for up to 48 h. This controlled release mechanism of incorporating nanoceria into gelatin enhances drug delivery to the ocular surface, thereby mitigating side effects.

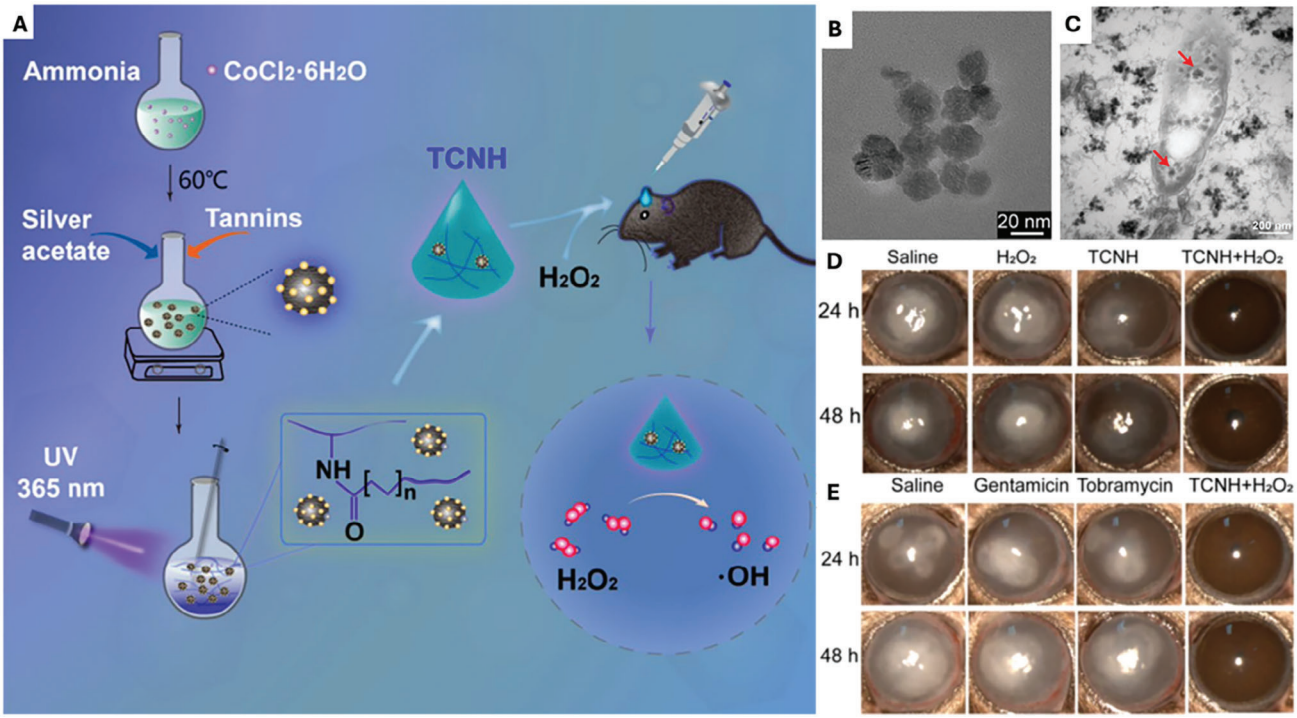

Figure 4. Nanozymes act as drug carriers for treating bacterial corneal infections. A) Schematic diagram illustrating the TCNH synthesis. B) TEM image of TCNH. C) Penetration of TCNH into P. aeruginosa, with red arrows indicating TCNH. D) Representative images of mouse eyes treated with TCNH, H_2O_2, or a combination thereof, where cloudiness indicated bacterial infection. E) Representative images of mouse eyes treated with antibiotics or TCNH+H_2O_2, with cloudiness indicating a bacterial infection. Adapted with permission. [80] Copyright 2023, Springer.

Another nanozyme drug carrier study was conducted by Wang et al.[80] to address bacterial infections in the cornea caused by *Pseudomonas aeruginosa* (P. *aeruginosa*). *P. aeruginosa* keratitis is an aggressive eye disease capable of causing complete corneal destruction within 24–48 h. Therefore, in addition to reducing oxidation and inflammation in the eye, it is crucial to develop anti-bacterial strategies to mitigate disease progression.[87] The authors developed a hybrid hydrogel (TCNH) by coordinating cobalt tetroxide (Co_3O_4) with tannin, which is known for its anti-oxidative and anti-bacterial properties (**Figure** 4A). The TCN NPs were crosslinked into a gelatin solution to enhance their biocompatibility and optical properties. TCN effectively penetrated *P. aeruginosa* owing to its small particle size (Figure 4B,C). It inhibited bacterial growth more efficiently than H_2O_2. Additionally, TCNH exhibited POD-like activity, generating highly toxic •OH in the presence of H_2O_2, contributing to its anti-bacterial and anti-biofilm properties. Free radicals can impair cell membranes and damage bacterial DNA and proteins by oxidizing cellular components or exhibiting oxidase-like activity responsive to pH changes.[17,88] The combination of H_2O_2 with TCNH had the most pronounced effect, suggesting an additive or synergistic effect with different mechanisms (Figure 4D). Moreover, TCNH demonstrated a more effective anti-microbial effect against a broad range of *P. aeruginosa* strains compared to antibiotics, indicating a potentially more effective chemical treatment approach for broad-spectrum anti-microbial purposes (Figure 4E). Similar anti-biofilm properties of nanozymes have been previously reported,[89] such as graphitic nanozymes,[17] ferumoxytol NPs,[88] and magnetic Fe_3O_4/SiO_2 NPs.[90]

4.1.3. Integrating Nanozymes with Polymeric Materials or Nanomaterials

Another application of nanoceria in DED involves the incorporation of nanozymes and polymeric materials. Zou et al.[81] developed branched poly(ethylene imine)-graft-poly(ethylene glycol) (bPEI-g-PEG), in which the amine group in PEI coordinates with nanoceria to form a water-soluble, highly biocompatible CNP@bPEI-g-PEG nanozyme (**Figure** 5A). Additionally, the cationic polymers enhanced the internalization of CNP@bPEI-g-PEG into the cells. Animal studies on DED induced by scopolamine hydrobromide in mice demonstrated that topical administration of CNP@bPEI-g-PEG reduced fluorescein staining of the cornea and upregulated goblet cell numbers in the conjunctiva (Figure 3B), comparable to 0.3% sodium hyaluronate eye drops. Ex vivo (Figure 3C) and in vitro studies in HCECs with H_2O_2-induced DED showed no cytotoxicity, increased ROS scavenging within 24 h, and dose-dependent SOD and CAT-like activities.

In 2024, Chu et al.[76] proposed that targeting inflammation alone may not be the most effective approach for alleviating DED, as it stems from a vicious cycle initiated by tear film and cell instability, coupled with hyperosmolarity and immune cell activation, ultimately leading to inflammation. Therefore, they designed dual-metal nanozymes that could target multiple pathways. FeMn-DA/NC consists of Fe and Mn atoms were distributed on the surface of nitrogen-doped carbon materials, adopting a configuration resembling a dodecahedron. After that, PEGylation was performed (**Figure** 6A,B). In vitro studies demon-

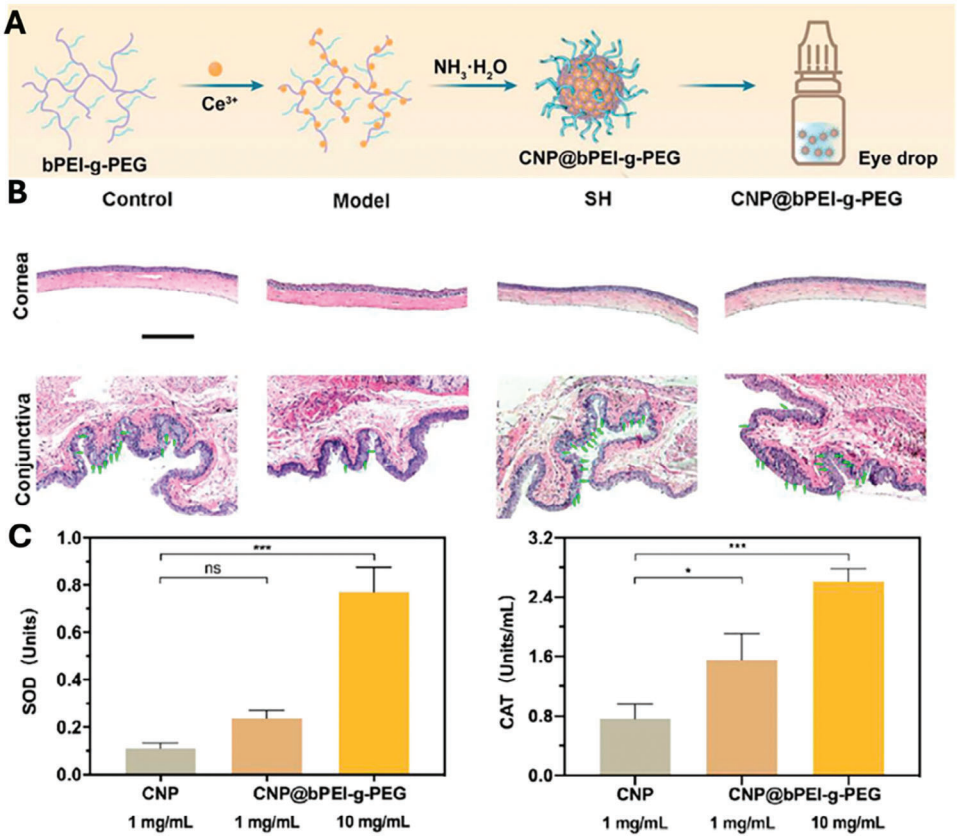

Figure 5. Nanoceria applications for DED. A) Schematic diagram showing the synthesis of CNP@bPEI-g-PEG Nanozymes. B) Hematoxylin and eosin (H&E) staining showing the morphology of the cornea and goblet cells (green arrows) in the conjunctiva after different treatments. C) Ex vivo study demonstrating enzyme-like actions of CNP@bPEI-g-PEG. Adapted with permission.[81] Copyright 2022, Oxford Academic.

strated that FeMn-DA/NC treatment decreased mitochondrial ROS levels and intracellular ROS production in a dose-dependent manner in HCE-2 cells in a hypertonic medium, restoring the anti-oxidative enzyme activity levels of SOD1, CAT, GPX1, and HO-1 to healthy levels (Figure 6C). FeMn-DA/NC also exhibited anti-apoptotic effects and suppressed the ROS/NLRP3 signaling axis involved in inflammation (Figure 6D,E). In a DED mouse model, a 7-days treatment with FeMn-DA/NC eye drops improved corneal integrity (Figure 6F), increased tear volume, and reduced ROS production and inflammatory marker expression in the cornea. Although the efficacy of FeMn-DA/NC did not surpass that of a commercial DED drug, cyclosporine A, it provides encouraging results that warrant further studies. Since this is the first dual-single-atom nanozyme for DED management, further investigation of biosafety is needed.

4.1.4. Integrating Nanozymes with Soft Materials

Two soft materials have recently been studied and incorporated with nanozymes to promote nanozyme delivery to the eye. The first one is CCLs. CCLs serve as valuable tools for ocular drug delivery and UV blockage, facilitating extended drug release to overcome corneal barriers that often result in poor drug absorption, rapid metabolism, and irreversible depletion. CCLs are commonly employed in the treatment of corneal diseases, like DED and damages caused by UVA radiation.[91] Liu et al.[62] recently fabricated CCLs using nanozymes to address corneal surface diseases. They embedded nanozymes from the PB family, known for anti-oxidative properties and biocompatibility, into hydroxyethyl methacrylate (HEMA) matrix materials through UV cross-linking (**Figure 7A**). By combining PB NPs and analogs (PBA), which were formed by coordinating Fe ions with Co^{2+}, Ni^{2+}, and Cu^{2+} precursors, they developed multi-color nanozyme-CCLs capable of scavenging ROS and protecting ocular tissues from UVA radiation or H_2O_2-induced damage in HCECs (Figure 7B,C). In animal models exposed to high levels of oxidative stress from H_2O_2 or UVA radiation, wearing multi-color nanozyme-CCLs for 2 days resulted in efficient protection of corneal tissues, including suppression of inflammation and restoration of corneal thickness. In this design, nanozyme-CCLs not only acted as a physical barrier to block external stimuli from the environment but also suppressed intraocular ROS production (Figure 7D). This diversity in the color of PBA could serve as a substitute for conventional pigments. This marks the second publication utilizing nanozymes in CCLs for ocular applications, following the study by Swaidan et al.[18] on H_2O_2 sensing using organic-inorganic hybrid nanoscale materials, CuS-BSA-$Cu_3(PO_4)_2$. Both studies have demonstrated the innovative use of nanozymes in CCLs for ocular purposes.

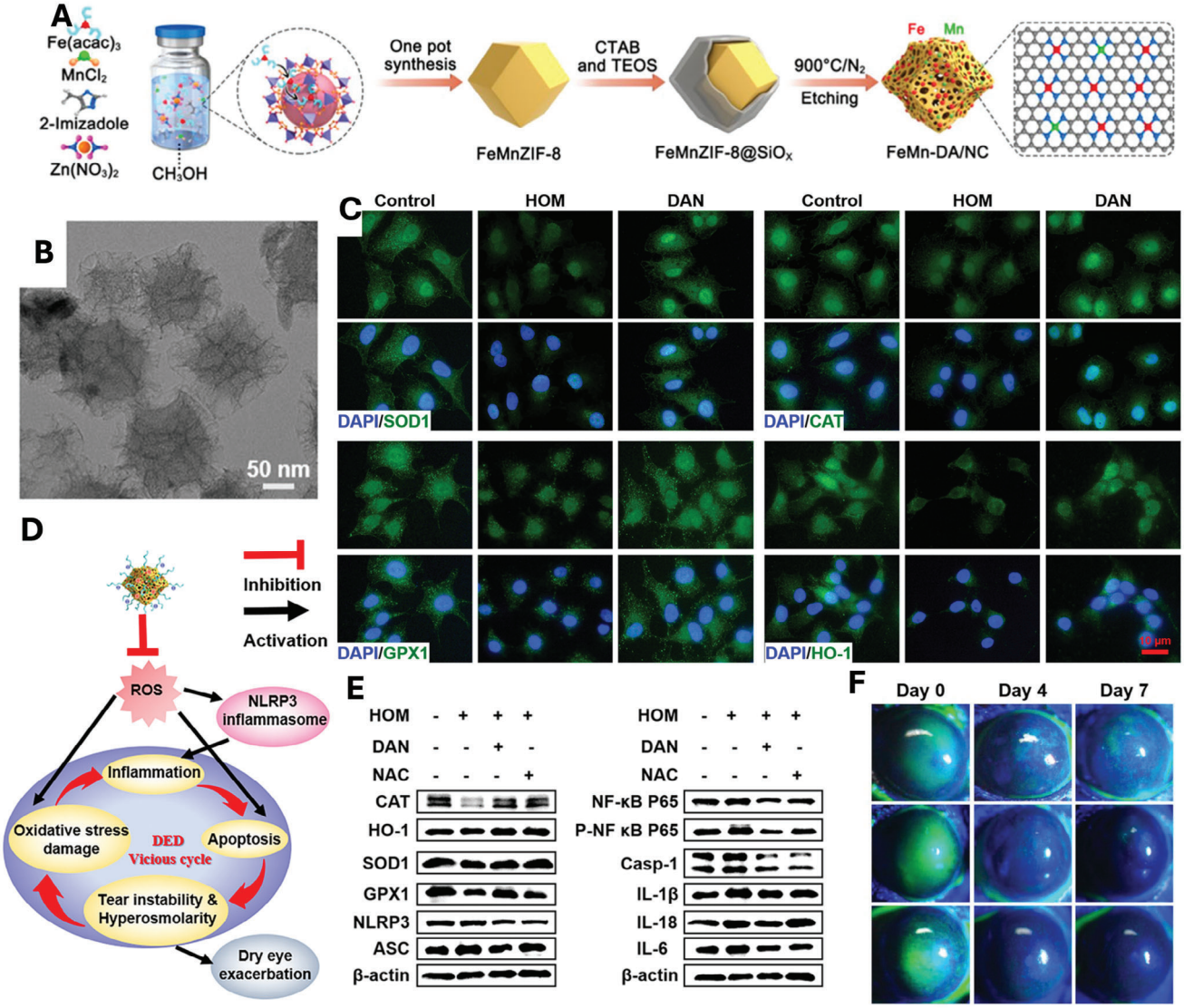

Figure 6. Dual-metal nanozyme eye drops for DED. A) Schematic diagram of the FeMn-DA/NC synthesis. B) TEM images reveal the morphology of FeMn-DA/NC. C) Immunofluorescence analysis of SOD1, CAT, GPX1, and HO-1 expression levels in HCE-2 cells. D) Schematic representation of the mechanism of action of FeMn-DA/NC in DED. E) Western blot results illustrate the expression levels of various inflammatory markers and proteins in the NLRP3 pathway. F) Fluorescein staining of DED mice after 4 or 7 days of topical treatment. Adapted with permission.[76] Copyright 2024, Springer.

The second application involved microneedles. Microneedles present a minimally invasive method for drug delivery and could offer notable benefits compared to conventional intravitreal injections in terms of patient acceptance and the potential for reduced eye damage. Therefore, it has been widely studied in skin or ocular applications.[19] Kong et al.[92] investigated the development of microneedles engineered to administer Fe-tannic acid nanozymes (FeTAP) within their tips to treat keratitis. Tannic acid is a natural water-soluble polyphenol compound, well-known for its anti-oxidative, anti-bacterial, and astringent properties. Additionally, the photothermal effect of the FeTAP microneedles induced a rapid temperature increase in the microneedles after penetration, enhancing their adaptation to soft tissues. By harnessing the pH-dependent POD-mimetic capabilities of FeTAP, the integrated microneedles generated elevated levels of •OH in acidic environments, effectively targeting bacteria. In a rat eye infection model, this formulation demonstrated superior therapeutic efficacy compared to traditional eye drops, microneedles without nanozymes, or nanozymes alone.[20]

In addition, Liu et al.[82] devised a method to address keratitis by creating microneedles containing Mn-based nanozymes. Initially, they synthesized graphdiyne (GDY) nanosheets with a 2D-layered porous nanostructure, offering attachment sites for metal ions (**Figure** 8A). The significant presence of alkyne bonds in GDY nanosheets facilitated the anchoring of Mn^{2+} ions and modulation of their electronic structure, forming MnOx/GDY complexes. These complexes were integrated into hyaluronic acid- and PMMA-based ocular microneedles (MGMN) for keratitis treatment. The microneedle design enabled the direct application of nanozymes to the cornea, enhancing targeted delivery

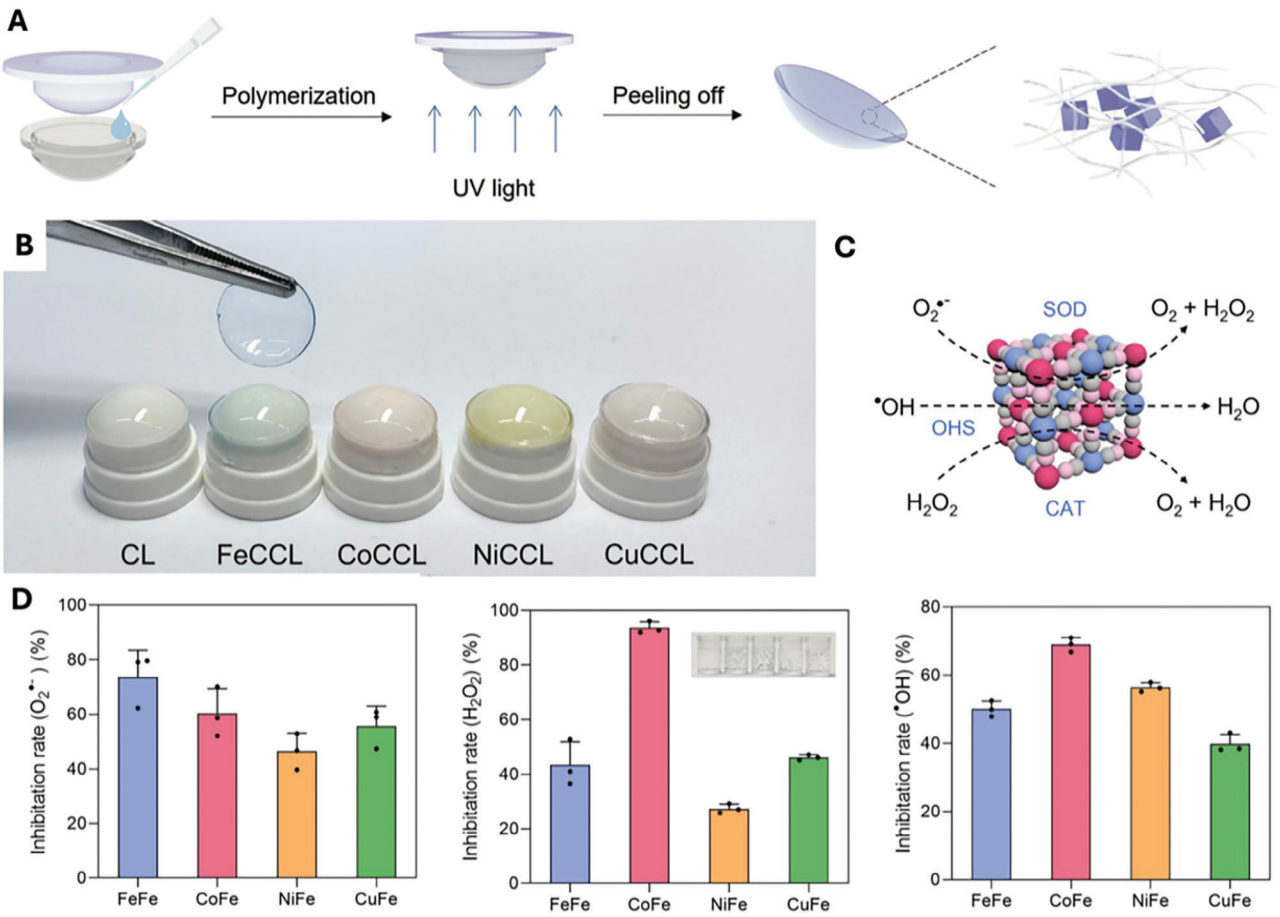

Figure 7. Nanozyme CCLs for corneal surface diseases. A) Fabrication of nanozyme-CCLs in which nanozymes were added before polymerization. B) Colors of CCLs with different compositions. C) Schematic diagram illustrating the potential mechanisms of nanozyme-CCLs. D) The ROS scavenging effect of different nanozyme-CCLs. Adapted with permission.[62] Copyright 2023, Wiley-Blackwell.

and therapeutic effectiveness (Figure 8B–F). MGMN exhibited anti-microbial and anti-inflammatory properties due to its multiple enzyme-like activities, including mimicking POD, CAT, and SOD. Furthermore, the microneedle system facilitated MGMN penetration through the ocular barrier, resulting in enhanced bioavailability. The experiments demonstrated that MGMN effectively eradicated pathogens, prevented the forming of biofilms, reduced inflammation, relieved ocular hypoxia, and promoted the integrity of corneal epithelium (Figure 8F).[82] This study underscores the potential of combining the microneedle technology with nanozymes to manage ocular diseases, offering a promising approach for precise drug delivery and improved therapeutic outcomes.

4.2. Nanozyme Treatment of Eye Diseases in the Posterior Segment

4.2.1. Nanozymes as a Drug Delivery Carrier

Jiang et al.[64] aimed to treat uveitis by designing Fe-curcumin nanozymes, in which metal coordination was formed between the Fe and phenol groups of curcumin, a natural product known for its anti-oxidative properties (**Figure 9A**).[93] This combination resulted in the suppression of cytokines including interferon (IFN)-γ, Interleukin (IL)−17, and TNF-α in lipopolysaccharide + IFN-γ-treated peripheral blood mononuclear cells. Simultaneously, it also reduced H_2O_2 levels and inhibited the differentiation of Th1 and Th17 immune cells (Figure 9B). In a rat model of uveitis induced by intraperitoneal injection of pertussis toxin in adult male Lewis rats, Fe-curcumin was administered orally for 11 consecutive days, with a single intravitreal injection on the 7th day to ensure delivery. Results indicated the presence of Fe-curcumin in the retina (Figure 9C) and decreased levels of inflammatory markers in both the eye and serum.[64] However, it remains uncertain whether oral administration of Fe-curcumin effectively delivered the drug to the retina, no drug delivery data before day 7 were available. Additionally, the lack of control groups, such as nanoceria or curcumin alone, makes necessity of using this MOF in comparison with existing treatments less obvious.

In 2023, Gui's group reported another Fe-based nanozyme for posterior diseases.[83] They synthesized ultrasmall coordination polymer nanodots, Fe-quercetin, to manage diabetic retinopathy through both prevention and treatment strategies. Their study

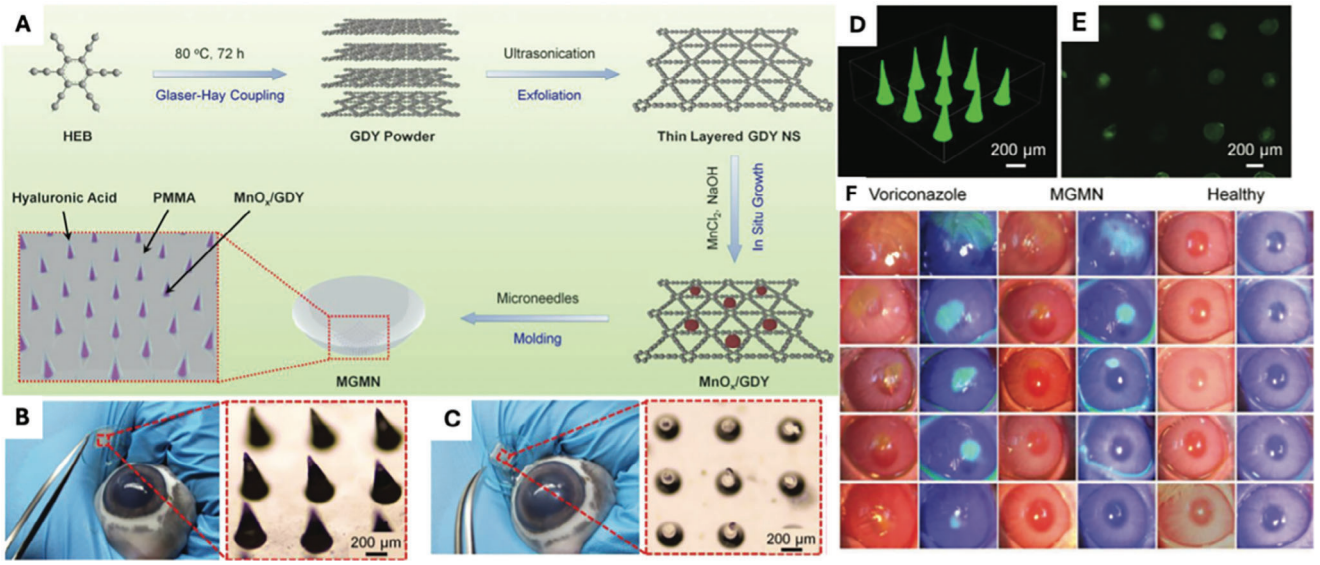

Figure 8. Mn-based nanozymes for treating microbial infections in the cornea. A) Schematic diagram illustrating MGMN synthesis. Images of MGMN B) before and C) after administration into a pig eye are shown, along with fluorescent images of FITC-labeled MGMN D) before and E) after administration into a pig eye. F) Representative images of the corneas of rabbits with fungal infection receiving various treatments on days 0, 3, 6, 9, and 12. Adapted with permission.[82] Copyright 2023, Springer.

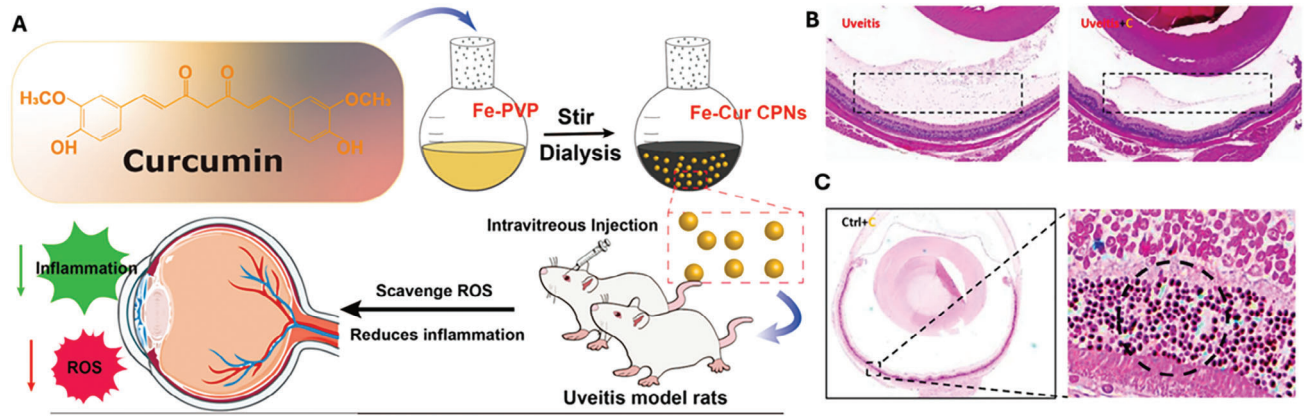

Figure 9. Nanozymes act as a drug delivery carrier for retinal diseases. A) Schematic diagram illustrating the synthesis of the Fe-curcumin nanozymes. B) H&E staining of the rat eyes. Boxes indicate areas with inflammatory factors. Left: control group. Right: treatment group. C) Retina with PB slices after the injection of Fe-curcumin nanozymes. The circle indicates the location of the Fe ions. Adapted with permission.[64] Copyright 2023, Springer Nature.

was comprehensive, encompassing synthesis, testing the therapeutic effects, and examining enzyme-like activities such as SOD, CAT, and POD activity of Fe-quercetin *ex vivo* and in vitro using high-glucose-induced monkey choroid-retinal endothelial cells and human umbilical vein endothelial cells, and in vivo in a rat model of streptozotocin-induced diabetic retinopathy. Additionally, they investigated the biodistribution of this nanozyme in the blood and retinas of rats. Transcriptome and mRNA splicing analyses were performed to elucidate the underlying mechanisms. This study demonstrated that the combination of the anti-oxidative natural molecule quercetin and Fe in coordination could form 10 nm nanodots that exhibit multifaceted effects. These nanodots effectively scavenged ROS in cells and prolonged their residence time in both serum and retina for up to 96 h after oral administration of Fe-quercetin, thereby demonstrating a promoted anti-angiogenic capacity in model rats. Transcriptome results indicate that Fe-quercetin can influence the downregulation of NF-κB, TNF, PI3K/Akt/mTOR, and other signaling pathways related to oxidative stress, inflammatory response, cell metabolism, proliferation, apoptosis, and neovascularization in diabetic retinopathy, suggesting their potential therapeutic efficacy. Owing to the ultra-small size of the nanodots, this study sheds light on the potential of oral administration of nanodots for drug delivery to the retina, bypassing the blood-retinal barrier. This approach could offer an alternative to intravitreal injections for the treatment of retinal diseases.

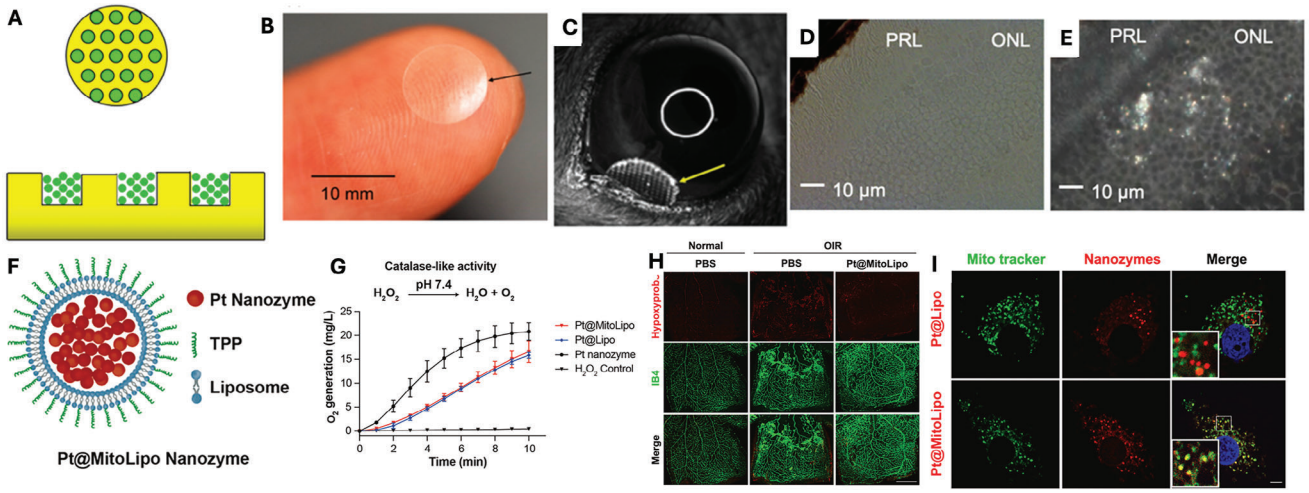

Figure 10. Integrating nanozyme with nanomaterials for retinal diseases. A) Schematic diagram illustrating the synthesis of Cerawafer. B) Cerawafer displayed on a fingertip. C) Application of Cerawafer on a mouse eye. D,E) Hyperspectral images show wafers with gold nanospheres (used as a control mimicking nanoceria) in the retina, depicted as white dots. Adapted with permission.[84] Copyright 2023, Springer Nature. F) Illustration of PtNPs encapsulated within MitoLipo for targeted delivery to mitochondria. G) Measurement of CAT-like activity of nanozymes in H_2O_2 solutions. H) Images comparing retinas of normal and OIR mice treated with Pt@MitoLipo nanozymes. I) Images showing colocalization of Pt@MitoLipo with mitochondria in cells. Adapted with permission. [85] Copyright 2022, Elsevier.

4.2.2. Integrating Nanozymes with Biomimetic Materials or Nanomaterials

The treatment of posterior segment eye diseases often requires invasive drug delivery methods to enhance the therapeutic efficacy and drug bioavailability. While there is currently no effective cure for AMD, the primary approach often involves slowing the progression of AMD through intravitreal injections of anti-VEGF treatment.[41b,45] However, there remains a need for effective therapeutic management with high patient compliance. Shin et al.[84] developed a 500 nm diameter wafer with nanocarriers printed on polyvinyl alcohol (PVA) (Cerawafer) to deliver nanoceria to the retina for managing AMD (**Figure 10**A,B). This is essentially a transparent polydimethylsiloxane (PDMS) patch printed with nanoceria. PVA, which is commonly used in artificial tears to maintain eye moisture, was incorporated to enhance the mucoadhesiveness of the PDMS patch. When applied to the lower part of the eye (Figure 10C–E), the nanoceria would be released and delivered to the retina in a non-invasive manner. The retention of the Cerawafer nanoceria in the retina lasted for more than a week. This application demonstrated the ability to suppress retinal neovascularization in a mouse model lacking the very-low-density lipoprotein receptor (vldlr−/−), which exhibits phenotypic characteristics mimicking the condition of patients with retinal angiomatous proliferation due to increased oxidative stress in the retina. The study illustrated the in vivo efficacy of Cerawafer in modulating ROS and associated downregulation of VEGF expression in the retina. Although the study showed the delivery of nanoceria to the retina, the precise delivery route remains unknown. Patches, microneedles, and inserts share similar mechanisms as feasible tools for ocular drug delivery. They can administer drugs through multiple routes including the corneal-conjunctival route or the sclera.[94] It is also hypothesized that the small size of nanoceria may aid in its passage through the ocular barrier, dispersing it throughout the eye and gradually reaching the retina. However, while the authors suggest that nanoceria can specifically target the retina, this assertion lacks clarity. Further research is necessary to fully understand the precise mechanism of nanoceria delivery to the retina and its targeting specificity.

Another application of Pt-based nanozymes was mitochondrial-targeting PtNPs liposomes (Pt@MitoLipo). Xue's group[85] developed an approach for reducing oxidative stress in mitochondria with Pt@MitoLipo nanozymes (Figure 10F). Pt-based nanozymes, mimicking SOD and CAT activities (Figure 10G), were coated with triphenylphosphonium (TPP)-conjugated liposomes for improved biocompatibility and cellular uptake. TPP enabled liposomes to cross cell membranes, bypass lysosomal degradation, and directly target mitochondria for precise detoxification of mitochondrial ROS and alleviation of hypoxia. Validation with human retinal endothelial cells (HRECs) showed effective mitochondrial localization in 2 h and restoration of membrane potential. In an oxygen-induced retinopathy mouse model, these nanozymes normalized neovascularization and VEGF expression levels (Figure 10H,I). In comparison to a similar study by Su's group, Xue's design utilized a 250 times higher concentration of PtNPs. However, neither study provided a rationale for the concentration of NPs they used. Further research might be needed to understand the optimal dosing and mechanistic underpinnings of Pt-based nanozymes in therapeutic applications.

The degradation of PRs in AMD is attributable to oxidative stress and the high metabolic activity of rods and cones, leading to cell death in the absence of sufficient anti-oxidative defense. Nanoceria has emerged as a promising candidate for AMD protection.[22] Cupini et al.[71] developed PtNPs coated with rat serum albumin (RSA-PtNPs), demonstrating their superior CAT-like activity compared to CeO_2 NPs, even at concentrations 5000 times lower (**Figure 11**A,B). Coating PtNPs with rat serum albumin, a prevalent protein in vitreous humor, enhanced their colloidal stability in biofluids. When injected into the eyes of

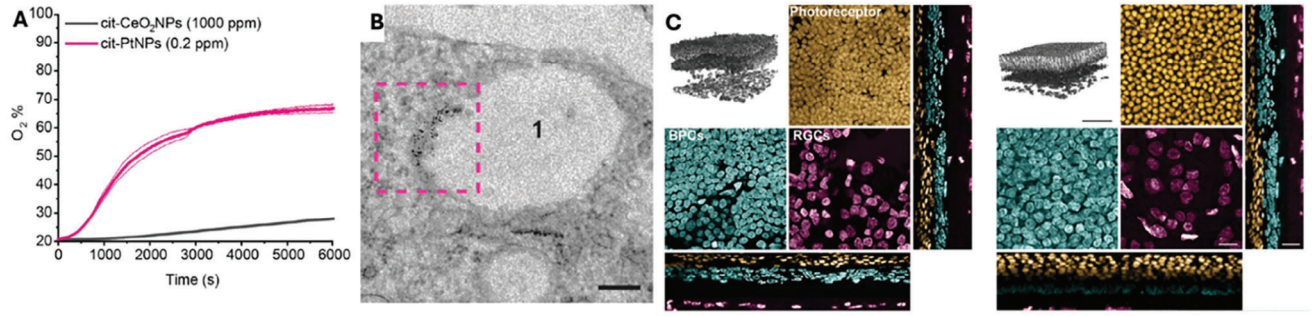

Figure 11. Integrating nanozymes with biomimetic materials for retinal diseases. A) Comparison of CAT-like activity between PtNPs and CeO_2NPs. B) Image showing PtNPs internalized by rat cortex neurons. C) 3D reconstruction of rat retinas treated with the delivery vehicle (left) and PtNPs (right) after light-induced damage. Adapted with permission.[71] Copyright 2023, American Chemical Society.

rats with light-induced AMD, RSA-PtNPs prevented or reduced photo-oxidative damages, maintained PR and retinal ganglion cell functionality, restored retinal structure (Figure 11C), and reduced inflammation, particularly when administered after damage onset. In a related study, Su et al.[95] investigated platinum nanozymes' ability to mitigate light-induced retinal damage. They found that PtNPs increased the expression of genes associated with anti-oxidative defense and influenced metabolic processes in the retina, preserving retinal cells from oxidative harm, involving the mTOR, PI3K-Akt and MAPK signaling pathways. These underscore platinum PtNPs' potential as an effective treatment for severe retinal diseases involving PR degeneration.

5. Summary and Future Directions

In this article, we reviewed the latest progress in using nanozymes for the treatment of ocular diseases. Unlike systemic delivery methods required for many other diseases, the eyes allow for direct local delivery due to their unique anatomy and exposure. While numerous NPs have been explored for treating ocular diseases, our focus was on nanozymes due to their multi-enzyme-like activities, prolonged resident time in the eye, and ease of modification and incorporation into various materials. At the same time, nanozymes can also be particle of drug delivery vehicles. Despite evidence of their efficacy in scavenging ROS and anti-microbial infections in ocular diseases, the clinical acceptance of nanozymes in ocular therapy remains limited.

Several concerns need to be addressed regarding their use. 1) Some nanozymes were used as bare materials, potentially leading to safety concerns such as systemic toxicity and long-term residence in the body due to their small sizes, lacking of degradation mechanism and leaching of metal species.[61] 2) Bare materials lack targeting or controlled release mechanisms, which may hinder efficacy and have side effects. 3) Recent studies have attempted to integrate soft materials or combine other NPs with nanozymes, such as microneedles, CCLs, and liposomes, to enhance efficacy, achieve controlled release, and reduce toxicity. However, their delivery routes and pharmacokinetics remain unclear. 4) Due to anatomical limitations, fewer research papers on nanozymes focus on ocular diseases in the posterior segment. A paper reviewed also includes intravitreal injection to ensure the delivery of nanozymes to the back of the eye in addition to oral administration.[64] 5) While most of the reviewed papers focused on the efficacy of nanozymes in ocular diseases, few addressed dose optimization or their enzyme-like kinetics. In our recent study, we demonstrated that more than 60% of the 240 nanozymes papers examined did not optimize their nanozyme-to-substrate ratio. This indicates that these experiments might not be conducted under kinetically favorable conditions.[96] Modifying the nanozyme-to-substrate ratio to achieve optimal catalysis conditions could potentially enhance the enzymatic reaction of nanozymes. 6) The molecular mechanisms underlying nanozymes with multi-enzyme activities remain unclear. For example, nanozymes mimicking CAT and POD may scavenge ROS in the eye but produce more ROS in bacteria. Understanding the exact molecular mechanisms of electron movements within nanozymes is crucial and requires further investigation under different conditions. 7) The predominant research efforts in nanozymes for ocular applications have centered on nanoceria. Nonetheless, the enzymatic effects of various nanozymes, including gold NPs[97] and titanium dioxide,[98] remain largely unexplored in the field of ocular research, despite their demonstrated therapeutic efficacy in ocular diseases. For example, gold NPs are known for their GOD and POD like activities. Previously, gold NPs were observed to hinder new abnormal blood vessel growth in the retina in a mouse retinopathy mode by inhibiting VEGF-mediated autophosphorylation of VEGFRs. Recently, reports have indicated that intravenously administered gold NPs can traverse the blood-retinal barrier without causing retinal toxicity.[97] Moreover, there is no investigation comparing the enzymatic effects of those nanozymes mentioned above in addressing eye conditions. Such a comparison would be valuable in discerning the most effective nanozymes for these applications. These considerations underscore the need for additional research to optimize the use of nanozymes in ocular therapy and overcome existing challenges before their widespread clinical adoption.

Based on the papers reviewed here, we propose some potential future directions in nanozymes research include 1) surface modification for "smart" enzyme-like activities, such as conjugating targeting ligands like aptamers to nanozymes,[99] which could enhance their retention on the ocular surface. Aptamer-functionalized liposomes have shown promising results in cornea tissue targeting,[100] suggesting similar approaches could be effective for nanozymes. 2) Development of light-responsive nanozymes: Given the eye's constant exposure to light, developing photoresponsive or light-activated nanozymes could

enable targeted delivery, particularly for light-induced ocular diseases. Research on light-activated nanozymes has already been published, indicating a promising avenue for exploration.[101] 3) Encapsulation in lipid bilayers: Encapsulating nanozymes with a lipid bilayer could improve their biocompatibility.[85] This approach may extend the applicability of POD-mimicking nanozymes, such as Fe_3O_4 NPs, which typically work efficiently only in acidic conditions. Encapsulating it in liposomes was reported to break the pH limit of its action.[102] However, encapsulation in liposomes may hinder access to large substrate molecules, necessitating careful testing of nanozymes activity under such conditions. 4) Conjugation with other molecules for synergistic effects: Conjugating nanozymes with other molecules, such as flavonoids or phenolic acids from natural products,[103] could lead to synergistic therapeutic effects. Nanozymes have the potential to bind to these molecules via coordination bonds, acting as delivery tools and therapeutics simultaneously. This approach holds promise for enhancing the efficacy of enzyme-based therapies for ocular diseases. By addressing these challenges and pursuing these avenues of research, we might unlock the potential of nanozymes for treating ocular diseases and improve patient outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

eyes, inflammation, nanozymes, ocular diseases, oxidation

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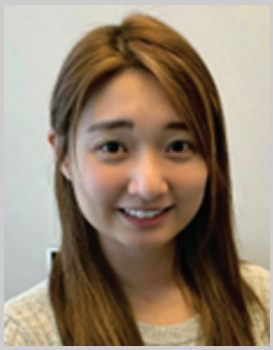

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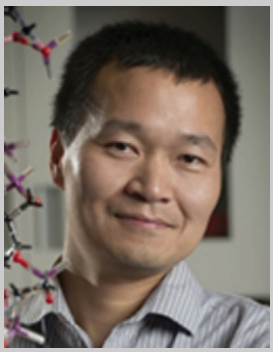

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