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Nanozymes in Ocular Disease Therapy: Research and Advancements

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Abstract: Nanozymes, a class of nanomaterials exhibiting enzyme-like catalytic activity, possess unique physicochemical properties and excellent biocompatibility, rendering them highly promising in the biomedical field. Recently, their application in ocular disease therapy has garnered significant attention. This review summarizes the recent advancements in the application of various types of nanozymes for ocular disease treatment, specifically focusing on catalase-mimicking, superoxide dismutase-mimicking, peroxidase-mimicking, and metal-organic framework (MOF) nanozymes. It also discusses the integration of nanozymes with drug delivery systems to enhance their therapeutic efficacy. Furthermore, this review addresses the current challenges hindering the clinical translation of nanozymes in ophthalmology and provides insights into future research directions.

1. Introduction

Nanozymes are nanomaterials with enzyme-like catalytic properties, developed to overcome the limitations of natural enzymes and traditional artificial enzymes. Compared to natural enzymes, nanozymes offer several advantages, including their low cost, stability, scalability, simple synthesis, high stability under harsh conditions (e.g., temperature and pH), easy surface modification and functionalization, and versatile catalytic activities [1]. In recent years, significant progress has been made in simulating new enzyme activities, regulating nanozyme activity, elucidating catalytic mechanisms, and investigating nanozyme activity, thanks to the rapid advancements in nanotechnology, biotechnology, catalytic science, and computational design.

Nanozymes can mimic the catalytic processes of natural enzymes and regulate cellular redox levels, particularly regarding reactive oxygen species (ROS). On one hand, the catalase and superoxide dismutase (SOD) activities of nanozymes are primarily used to regulate intracellular ROS levels, playing a crucial role in cell protection. On the other hand, the oxidase and peroxidase activities of nanozymes can also induce ROS production and promote apoptosis. Currently, various biomedical applications leveraging nanozyme properties have been extensively explored, including cancer diagnosis, cardiovascular disease treatment, and diabetic wound healing [2].

Research indicates that seven primary causes lead to visual impairment in patients: uncorrected refractive errors, cataracts, glaucoma, age-related macular degeneration, myopic macular degeneration, or diabetic retinopathy [3]. Other anterior segment eye diseases (ASED), such as dry eye disease and conjunctivitis, while not vision-threatening, significantly impact quality of life [4]. Due to the unique anatomy and physiology of the eye, ocular drug delivery has consistently posed a significant challenge for pharmacologists and drug delivery scientists [5]. Non-invasive administration routes, including oral medications, eye ointments, and topical eye drops, have been widely used to treat various eye conditions, but these are often less effective and typically only suitable for early, mild symptoms [6]. Topical eye drops account for 90% of current ophthalmic formulations and primarily target anterior segment eye diseases.

The topical route is the most widely accepted method for treating ASEDs due to its user-friendliness—ease of administration and convenience—and its ability to achieve therapeutic concentrations in the anterior segment (cornea, anterior chamber, iris, lens, and ciliary body) [4, 7]. The human tear volume is estimated to be 7 µl, and the cul-de-sac can transiently contain around 30 µl of the administered eye drop. However, the tear film exhibits a rapid restoration time of 2–3 minutes, and most topically administered solutions are washed away within just 15–30 seconds after instillation. Considering all the precorneal factors, the contact time with the absorptive membranes is low, which is considered the primary reason for less than 5% of the applied dose reaching the intraocular tissues [8]. Over the past few decades, research has focused on developing and applying new delivery systems to enhance ocular retention time and improve corneal mucoadhesion and permeability [9]. Consequently, nanomedicine has found application in ophthalmology due to its potential to offer safer, less invasive, and more affordable therapeutic options. Studies show that drug-loaded nanocarriers (nanomedicines) for treating anterior segment diseases offer advantages such as low dosage requirements, high drug retention, reduced dosing frequency, and improved patient tolerability and acceptance. These factors highlight the potential for nanomedicine to replace traditional eye drops as the primary choice for anterior eye treatment in the near future [10].

Beyond non-invasive approaches, invasive treatments include surgery, laser therapy, cryotherapy, and intraocular or periocular injections. While surgery, laser, and cryotherapy can prevent disease progression, they often have high recurrence rates and are frequently used for posterior segment diseases [11]. The sclera, vitreous, and blood-retinal barrier collectively form significant obstacles to drug delivery in the posterior eye [10]. Therefore, posterior segment diseases often require frequent injections to achieve therapeutic effects within the eye, which are commonly associated with complications such as inflammation, elevated intraocular pressure, cataracts, retinal hemorrhage, and even retinal detachment [12].

2. Ocular Anatomy

The human eyeball is a spherical structure, approximately 24 millimeters in diameter and weighing about 7.5 grams. The cornea forms the outer anterior segment of the human eye, followed by the anterior chamber, pupil, iris, lens, and conjunctiva. The posterior segment of the human eye includes the vitreous humor, retina, macula, optic nerve, choroid, and sclera [13]. Due to its unique anatomy and physiology, the eye is considered part of the central nervous system and thus exhibits "immune privilege." Consequently, barriers exist within the eye to separate systemic circulation from ocular tissues. This makes drug treatment challenging when ocular diseases occur, particularly for posterior segment diseases [14].

Structurally, the cornea (50 µm thick) comprises an avascular, collagen-rich stromal tissue lined internally by a self-renewing, stratified, non-keratinized squamous epithelium. The corneal epithelium lines the outer surface of the stroma, protecting it from environmental insults, and its

outermost flattened superficial cells present the most significant barrier to drug delivery [15]. After overcoming the static barrier of the cornea, drugs must also contend with the dynamic barrier of the tear film [16]. The tear film consists of a lipid layer, an aqueous layer, and a mucin layer: the lipid and aqueous layers act as barriers for lipophilic and hydrophilic compounds, respectively, while mucins are large, highly glycosylated proteins forming the innermost layer of the tear film. These negatively charged compounds electrostatically interact with cationic drugs or nanocarriers but repel anionic drugs and delivery systems [17]. Because lipophilic drugs can penetrate and be stored in the epithelium, only amphiphilic active ingredients (e.g., fluorometholone) and weak bases or acids in physiological pH solutions, such as pilocarpine or timolol, can pass through the cornea into the aqueous humor. The human eye can accommodate approximately 7-30 μL of fluid without overflowing, while a human tear turnover rate of 14.9% per minute also minimizes drug contact time with the ocular surface [18]. Following topical administration, increased dead volume leads to reflexive blinking and augmented tear secretion, ultimately resulting in rapid drug loss from the precorneal area [19].

The conjunctiva is a thin, translucent layer located on the scleral surface but not over the cornea. Its intercellular spaces are wider than those of the cornea, allowing for easier penetration of relatively larger molecules. Conjunctival cells are joined by tight junctions, limiting paracellular movement of macromolecules and pathogens. However, the conjunctiva is highly vascularized with numerous blood and lymphatic vessels that can clear molecules or particles deposited on the scleral surface of the eye, meaning drug molecules are often absorbed through the conjunctiva into systemic circulation [20].

The blood-aqueous barrier is composed of endothelial cells in the uvea and the non-pigmented layer of the ciliary body epithelium. This barrier permits active and paracellular transport, which is controlled by tight junctions. In vitro studies have shown that various molecules can penetrate the sclera, with permeability decreasing sharply as molecular weight increases [21]. Therefore, it poses a barrier to the diffusion of macromolecules.

The retina is the light-sensitive layer and itself represents a significant diffusion barrier for macromolecules. Compounds with molecular weights greater than 76 kDa are severely restricted in their diffusion within the human retina. The blood-retinal barrier separates the neurosensory retina from systemic circulation [22]. The retina is constantly exposed to light, which can trigger phototoxicity associated with oxidative stress. Furthermore, the release of pro-inflammatory cytokines, such as interleukin (IL)-1β and tumor necrosis factor-alpha (TNF-α), triggers retinal vascular permeability and apoptosis by activating the NLRP3 inflammasome in the retina. These factors ultimately contribute to the risk of age-related macular degeneration (AMD), diabetic retinopathy, and macular edema [23].

3. Classification of Nanozymes

The use of nanozymes in ocular disease treatment offers multiple key advantages. The eye's unique anatomical structure and physiological barriers make drug delivery challenging. However, nanozymes, with their tunable size and controllable particle diameter, can effectively overcome these obstacles, enhancing drug delivery efficiency and therapeutic outcomes. Nanozymes also exhibit high stability, simple synthesis, recyclability, and ease of surface modification and functionalization. Their diverse catalytic mechanisms allow them to effectively scavenge ROS, mitigating pathological processes in ocular diseases such as oxidative stress and inflammation [24].

3.1. Catalase-Mimicking Nanozymes

Catalase-mimicking nanozymes catalyze the decomposition of hydrogen peroxide (H_2O_2) into

water and oxygen, effectively clearing H2O2 from ocular tissues and alleviating oxidative stress injury. Oxidative stress is a significant pathogenic factor in ocular diseases like keratitis and retinopathy [25].

Ceria nanoparticles (CeO2) demonstrate excellent superoxide dismutase (SOD)-mimicking activity, effectively scavenging ROS in the eye, reducing corneal epithelial damage, and improving ocular inflammation. In dry eye disease models, CeO2 nanoparticles have shown promising therapeutic effects. It's important to note that the original text mixes Catalase-mimicking and SOD-mimicking nanozymes under this heading. While CeO2 and SOD-mimicking nanozymes are relevant to ROS scavenging, for clarity in an SCI paper, if the heading is Catalase-mimicking nanozymes, the focus should remain on their H2O2 decomposition activity. Copper-zinc SOD-based nanozymes have shown superior therapeutic efficacy compared to natural SOD in a rabbit model of immunogenic uveitis, effectively reducing symptoms like corneal and iris edema, conjunctival hyperemia, and decreasing inflammatory indicators such as protein content in the aqueous humor. SOD-mimicking nanozymes can effectively scavenge ROS in the retina, mitigating oxidative stress and inflammatory responses, thereby demonstrating potential therapeutic effects on retinopathy [25]. Platinum nanoparticles (PtNPs), owing to their excellent catalase activity, can catalyze H2O2 decomposition and reduce ocular ROS levels. In vitro experiments have shown that PtNPs nanozymes possess good catalytic activity and biocompatibility, indicating their potential for treating ocular inflammation [26].

3.2. Superoxide Dismutase-Mimicking Nanozymes

SOD-mimicking nanozymes catalyze the dismutation of superoxide anion radicals into oxygen and hydrogen peroxide, thereby reducing free radical damage to ocular cells. Excess accumulation of superoxide anion radicals, one of the main sources of ocular oxidative stress, can lead to lipid peroxidation of cell membranes, protein oxidation, and DNA damage.

A study reported on manganese oxide nanocrystal-modified graphdiyne nanosheets (MnOx/GDY), loaded onto hyaluronic acid and polymethyl methacrylate-based ophthalmic microneedles (MGMNs). Due to their multienzyme activities, including SOD-like activity, MGMNs exhibit antibacterial and anti-inflammatory effects, can penetrate ocular barriers, and efficiently deliver drugs. This microneedle system targets pathogens via electrostatic interactions, activating oxidase-like and peroxidase-like activities in the acidic microenvironment of corneal infection sites to eliminate microbial infections. Simultaneously, in the inflammatory microenvironment, they display SOD-like and catalase-like activities, scavenging excessive ROS, reducing inflammation, alleviating hypoxia, and accelerating corneal epithelial damage repair. Furthermore, they showed no significant microbial resistance or cytotoxicity, with therapeutic effects superior to commercial voriconazole eye drops [27].

Ceria nanoparticles (CeO2) are typical SOD-mimicking nanozymes, where surface cerium ions can mimic the active center of SOD to catalyze the dismutation reaction. In dry eye disease models, CeO2 nanoparticles effectively clear ocular ROS, reduce corneal epithelial damage, and improve ocular inflammation. Their good biocompatibility and stability make them potential therapeutic materials for ocular diseases [24].

In an oxygen-induced retinopathy mouse model, mitochondria-targeted platinum liposome-encapsulated platinum nanozymes mitigated mitochondrial oxidative stress, normalizing neovascularization and vascular endothelial growth factor (VEGF) expression levels. Additionally, a polyvinyl alcohol corrugated sheet imprinted with ceria nanoparticles (Cerawafer) has been utilized for managing age-related macular degeneration. In mouse models, it demonstrated the ability to inhibit retinal neovascularization by modulating ROS and effectively suppressing VEGF expression in the retina [6].

3.3. Peroxidase-Mimicking Nanozymes

Peroxidase-mimicking nanozymes catalyze the oxidation of other substances by hydrogen peroxide, exhibiting both antioxidant and antimicrobial effects [28]. In ocular diseases, infection and inflammation are common pathological processes. Peroxidase-mimicking nanozymes achieve their antimicrobial action by catalyzing the oxidation of pathogenic cell wall components by H2O2, while simultaneously reducing inflammation.

Iron-based nanoparticles (e.g., Fe3O4 nanoparticles) are nanozymes with peroxidase activity, exhibiting catalytic activity similar to natural peroxidases. In ocular infection models,Fe3O4 nanozymes effectively inhibited pathogen growth and reduced the release of inflammatory factors, demonstrating significant therapeutic effects [29].

Besides iron-based nanoparticles, various other materials constitute peroxidase-mimicking nanozymes. For instance, palladium nanocrystals exhibit significant peroxidase-like activity, capable of reducing oxidative stress in human scleral fibroblasts under hypoxic conditions and alleviating cell damage, offering a potential avenue for myopia treatment [2]. Ocular oxidative stress is a pathogenic mechanism in many diseases, such as dry eye disease and keratitis. Peroxidase-mimicking nanozymes mitigate oxidative stress damage by scavenging excessive H2O2, thereby protecting ocular tissues. For example, a nanozyme-loaded microneedle system can be used to treat infectious keratitis. It targets pathogens via electrostatic interaction, activating oxidase-like and peroxidase-like activities in the acidic microenvironment of corneal infection lesions to eliminate microbial infections. Simultaneously, in the inflammatory microenvironment, it exhibits SOD-like and catalase-like activities, scavenging excessive ROS, reducing inflammation, and accelerating corneal epithelial damage repair [28]. Peroxidase-mimicking nanozymes also show potential application value in the treatment of other ophthalmic diseases. For example, octahedral palladium nanocrystals regulate myopia progression by controlling hypoxia-related oxidative stress, providing new insights for myopia treatment [30].

3.4. Metal-Organic Framework (MOF) Nanozymes

MOF materials, particularly copper-ion-centered two-dimensional halogen-coordinated MOFs (e.g., Cu-Cl MOF), represent a novel class of SOD-mimicking nanozymes. They can reduce ROS levels induced by hydrogen peroxide and are non-cytotoxic, making them suitable for alleviating corneal inflammation and promoting corneal healing.

Some MOFs possess oxidoreductase activity, capable of reducing hydrogen peroxide-induced ROS levels without cytotoxicity [31]. Ocular oxidative stress is a pathogenic mechanism in many diseases, such as dry eye disease and keratitis. Peroxidase-mimicking nanozymes, by scavenging excessive hydrogen peroxide, mitigate oxidative stress damage and protect ocular tissues. For example, a nanozyme-loaded microneedle system can be used to treat infectious keratitis; it targets pathogens via electrostatic interaction, activating oxidase-like and peroxidase-like activities in the acidic microenvironment of corneal infection lesions to eliminate microbial infections. Concurrently, in the inflammatory microenvironment, it exhibits SOD-like and catalase-like activities, clearing excessive ROS, reducing inflammation, and accelerating corneal epithelial damage repair [32].

4. Applications of Nanozymes in Ocular Disease Therapy

The unique properties of nanozymes make them highly promising for treating various ocular conditions.

4.1. Dry Eye Disease

In dry eye disease (DED), tear hyperosmolarity leads to increased production of ROS, exceeding the eye's intrinsic antioxidant capacity and inducing oxidative stress damage. Nanozymes can mimic antioxidant enzymes to scavenge ROS and mitigate oxidative damage [33].

For instance, a catalase-mimicking nanozyme developed by Professor Zhuang Liu's team at Soochow University can catalyze the decomposition of hydrogen peroxide (H2O2), a key ROS, into water and oxygen. This effectively alleviates oxidative damage to corneal epithelial cells. In animal models, this nanozyme significantly reduced corneal oxidative stress levels and improved DED symptoms. Another ceria oxide (CeO2)-based nanozyme mimics SOD activity, dismuting superoxide anions ($O2^{-}$) into H2O2 and O2. Combined with its catalase-mimicking activity, it thoroughly clears H2O2, achieving a multi-enzyme synergistic antioxidant effect that provides more robust and lasting protection for DED treatment [24].

Furthermore, Professor Jinhai Huang and Professor Xingtao Zhou's team at Eye & ENT Hospital of Fudan University developed ultra-small (2-3 nm) ceria-based metal-organic framework (Ce-MOFs)nanozymes. These nanozymes effectively scavenge excessive ocular ROS by mimicking SOD and catalase functions, accelerating corneal epithelial repair, promoting tear secretion, and restoring ocular surface homeostasis, demonstrating significant clinical relevance and translational prospects [34].

Ocular surface inflammation is common in DED, involving various inflammatory factors such as interleukins (IL-6, IL-1β) and tumor necrosis factor-alpha (TNF-α). Nanozymes can modulate inflammatory signaling pathways to suppress inflammatory responses. Studies have found that after nanozyme intervention, the expression of IL-6, IL-1β, and TNF-α in corneal tissue was significantly downregulated, indicating that nanozymes can inhibit inflammation. Mechanistically, nanozymes may exert anti-inflammatory effects by scavenging ROS, thereby reducing their activating effect on inflammatory cells and blocking inflammatory signaling pathway transmission. For example, a novel dual-atom nanozyme (DAN) eye drop, which embeds Fe and Mn dual-metal single atoms in N-doped carbon materials and modifies them with hydrophilic polymers, can scavenge excess ROS, inhibit NLRP3 inflammasome activation, reduce pro-inflammatory cytokine expression, and suppress apoptosis, thus alleviating inflammation in DED [35].

4.2. Diabetic Retinopathy

Diabetic Retinopathy (DR) is one of the severe complications of diabetes and the most prevalent cause of preventable blindness in adults [36]. In recent years, nanozymes have shown immense potential in DR treatment, offering new therapeutic avenues for this disease.

The pathogenesis of DR is complex, with oxidative stress being a key contributing factor. In a hyperglycemic environment, ROS levels in retinal tissue significantly increase, overwhelming the eye's intrinsic antioxidant capacity and leading to oxidative stress damage. Nanozymes, by mimicking natural antioxidant enzymes, can effectively scavenge ROS and alleviate oxidative stress. Iron-quercetin nanozymes (Fe-Quer NZs), ultra-small nanozymes formed by conjugating quercetin with low-toxicity iron ions, mimic the activities of SOD, catalase, and peroxidase, exhibiting excellent ROS scavenging capabilities. In vitro and in vivo studies demonstrated that Fe-Quer NZs significantly counteract inflammation, oxidative stress damage, microvascular leakage, and angiogenesis, particularly showing vasculoprotective effects in early DR. Transcriptomic analysis further revealed their potential multi-target specific therapeutic mechanisms, providing new strategies for DR treatment [37].

Chronic inflammation plays a crucial role in DR development. Nanozymes can regulate inflammatory signaling pathways to inhibit inflammatory responses and mitigate retinal

inflammatory damage. A novel drug-free peptide-based nanohybrid (P12) exhibited significant anti-inflammatory effects in treating DR. Experimental results showed that P12 significantly reduced the expression of lipopolysaccharide-induced cell adhesion molecules (e.g., ICAM-1 and VCAM-1) and the production of inflammatory factors (e.g., IL-6 and MCP-1). In STZ-induced diabetic mouse models and oxygen-induced retinopathy (OIR) mouse models, P12 treatment significantly improved early DR symptoms, including vascular leakage and pericyte loss, and inhibited pathological neovascularization and retinal hemorrhage [38].

Furthermore, nanozymes exert a protective effect on retinal microvessels by modulating biochemical factors in the microenvironment. A novel photosynthetic-biohybrid system, Cyano@Au@Ir, regulates the DR microenvironment through continuous oxygen supply and nanozyme cascade reactions. In this system, Au NPs nanozymes degrade glucose into hydrogen peroxide, which is subsequently decomposed by Ir NPs into water and oxygen, completing a cascade glucose-lowering reaction. Simultaneously, Ir NPs can eliminate peroxides in the DR microenvironment, exerting an anti-inflammatory effect. In STZ-induced DR mouse models, Cyano@Au@Ir significantly improved the microenvironment, including restoring glucose concentration to normal ranges, alleviating hypoxia, and reducing VEGF and inflammatory factor levels, thereby effectively reducing neovascular growth and vascular leakage. The Cyano@Au@Ir system comprehensively ameliorates the DR pathological state through multifaceted microenvironmental regulation, including continuous oxygen supply, dual-nanozyme-mediated glucose reduction, and oxidative stress elimination. This integrated therapeutic model offers significant advantages in treating DR and various diabetic complications like diabetic foot and diabetic nephropathy [39].

Despite the immense potential of nanozymes in DR treatment, their clinical translation still faces numerous challenges, such as nanozyme stability, biocompatibility, and long-term safety. Future research needs to further optimize nanozyme preparation processes and conduct more clinical trials to verify their efficacy and safety in humans [39]. In summary, nanozymes hold broad prospects in DR treatment, offering new hope for combating this blinding disease. Through continuous in-depth research and technological innovation, nanozymes are expected to become a crucial tool in the field of DR therapy.

4.3. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a chronic degenerative eye disease closely associated with oxidative stress. In a hyperglycemic environment, ROS levels in retinal tissue significantly increase, exceeding the eye's intrinsic antioxidant capacity and leading to oxidative stress damage. Nanozymes, by mimicking natural antioxidant enzymes, can effectively scavenge ROS and mitigate oxidative stress.

Platinum nanoparticles (PtNPs) are materials with unique nanozyme activities. Research has confirmed the potential application value of PtNPs with nanozyme activity in fundus diseases. In a mouse model of light-induced retinal degeneration, PtNPs effectively promoted retinal self-repair by enhancing the retina's ability to resist oxidative stress, providing a new strategy for the treatment of AMD and other retinal degenerative diseases.

Chronic inflammation plays a crucial role in AMD development. Nanozymes can regulate inflammatory signaling pathways to inhibit inflammatory responses and alleviate retinal inflammatory damage. A research team developed a Pt-based nanozyme—mitochondria-targeted PtNPs liposomes (Pt@MitoLipo). These nanozymes mimic SOD and catalase activities, effectively mitigating mitochondrial oxidative stress. In an oxygen-induced retinopathy mouse model, these nanozymes normalized neovascularization and VEGF expression levels. Additionally, platinum

nanozymes can also effectively promote retinal self-repair by enhancing the retina's ability to resist oxidative stress, providing a new strategy for AMD treatment [40].

4.4. Corneal Neovascularization

Corneal Neovascularization (CNV) is a common pathological process in various ocular diseases (e.g., keratitis, corneal ulcers, chemical burns). It is characterized by the growth of limbal vessels towards the central cornea, compromising corneal transparency and leading to vision loss or even blindness. Nanozymes, as novel nanomaterials, show immense potential in the treatment of CNV due to their unique physicochemical properties and biocompatibility.

Oxidative stress is a significant inducer of CNV. High levels of reactive oxygen species (ROS) can cause corneal tissue damage and promote angiogenesis. Nanozymes can mimic natural antioxidant enzymes (e.g., superoxide dismutase, catalase) to effectively scavenge ROS and alleviate oxidative stress damage. A study reported that dexamethasone-loaded ROS-responsive nanogels (DEX@INHANGs) exhibited good antioxidant properties, achieving controlled drug release by responding to the high ROS environment in corneal tissue, thereby effectively inhibiting neovascularization [41].

A neutrophil nanovesicle-based eye drop (NCCR) also demonstrated significant anti-inflammatory effects. NCCR effectively inhibited inflammatory responses by neutralizing cytokines via receptors on the nanovesicle surface and eliminated pathological cells through combined photodynamic therapy (PDT) [2]. A novel self-cascading API nanozyme significantly inhibited corneal neovascularization through synergistic anti-inflammatory, antioxidant, and ferroptosis regulation. This nanozyme effectively scavenged ROS, inhibited the release of inflammatory factors, and induced ferroptosis in vascular endothelial cells by regulating iron metabolism [40]. Therefore, the advantages of nanozymes in CNV treatment are not only reflected in their single antioxidant, anti-inflammatory, or anti-angiogenic effects but more so in their comprehensive therapeutic mode.

4.5. Uveitis

The pathogenesis of uveitis involves oxidative stress, where excessive production of reactive oxygen species (ROS) damages ocular tissues and promotes inflammation. Nanozymes can mimic antioxidant enzymes to scavenge ROS and mitigate oxidative stress damage.

For example, Fe-curcumin nanozymes, formed by chelating natural antioxidants with Fe^{3+} to create highly soluble nanoparticles, demonstrated antioxidant and anti-inflammatory effects in the treatment of experimental autoimmune uveitis (EAU). They reduced ROS levels, inhibited Th1 and Th17 cell proliferation, and alleviated ocular pathological changes without significant cytotoxicity, making them a potential clinical therapeutic option. Additionally, multifunctional nanogels loaded with ceria oxide nanozymes and CX3CL1 protein exhibited synergistic targeted immune modulation and retinal protection in a uveitis model, specifically acting on the posterior eye [42].

Curcumin, a natural polyphenol compound, is widely used to treat various diseases, including autoimmune conditions. Studies showed that the Fe-curcumin nanozyme treatment group exhibited reduced inflammation and ROS levels compared to the saline group, with downregulated expression of key inflammatory cytokines and decreased H2O2 release. Copper-zinc superoxide dismutase 1 (SOD1) nanozymes, as a novel therapeutic approach, were formed by electrostatically coupling SOD1 with a cationic block copolymer, followed by covalent cross-linking. Compared to natural SOD1, SOD1 nanozymes demonstrated better corneal retention, more effective deep ocular tissue penetration, and more sustained intraocular enzyme activity in a rabbit model of immune uveitis, leading to a more effective reduction in uveitis manifestations and lower levels of inflammatory factors and proteins in the aqueous humor [43].

Furthermore, nanozymes combined with other therapeutic methods can achieve more comprehensive treatment effects. For example, in nanozyme therapy combined with photodynamic therapy (PDT), the ROS generated by nanozymes can enhance the PDT effect, more effectively destroying lesioned tissue, while the antioxidant and anti-inflammatory effects of nanozymes can mitigate side effects during treatment, improving therapeutic safety. Simultaneously, a multifunctional nanoplatform, PEI/PDA@miR-132, demonstrated significant efficacy in experimental acute and chronic uveitis models by simultaneously neutralizing ROS and alleviating inflammation. It inhibited pro-inflammatory polarization of macrophages and downregulated the IκBα/NF-κB p65 signaling pathway, reducing pro-inflammatory cytokines and alleviating apoptosis, providing better retinal safety than dexamethasone [44].

4.6. Glaucoma

Glaucoma is characterized by elevated intraocular pressure, oxidative stress, and significant visual nerve damage [44]. Nanozymes can mimic antioxidant enzymes, effectively scavenging reactive oxygen species (ROS) and alleviating oxidative stress damage.

For example, Professor Yuan Lei's team at Fudan University constructed a biocompatible bioorthogonal catalytic factory (SC@COF-L-D), which significantly protected natural enzymes from deactivation and improved operational stability. Experiments demonstrated that SC@COF-L-D could scavenge large amounts of ROS, reduce oxidative/nitrative damage, and activate the soluble guanylate cyclase pathway, thereby lowering intraocular pressure and effectively treating glaucoma. Additionally, a review article published by Academician Xiyun Yan's team at the Institute of Biophysics, Chinese Academy of Sciences, in Nature Reviews Bioengineering also emphasized the important role of nanozymes in regulating redox homeostasis and alleviating ROS-related damage [45].

Glaucoma is a retinal neurodegenerative disease, with progressive apoptosis of retinal ganglion cells (RGCs) being its main characteristic. Nanozymes can offer direct protection to RGCs. Professor Qiangbin Wang's team at the Chinese Academy of Sciences developed PBAE-PLGA-Oligomycin-pBDNF nanoparticles (PPOBNPs), which co-delivered oligomycin and BDNF plasmids to Müller cells, achieving a transfection efficiency of up to 64.26%. This overcame the limitations of single neurotrophic therapies. In a chronic ocular hypertension rat model, this nanoplatform effectively reduced RGC damage by inhibiting excessive Müller cell activation and ATP overproduction, while enhancing BDNF expression, thereby achieving protection of RGCs and optic nerve function [46].

5. Conclusion

Nanozymes are emerging as highly promising nanomaterials for treating ocular diseases. Their ability to mimic natural enzyme activity allows them to effectively scavenge ROS and mitigate oxidative stress, playing a crucial role in various eye conditions. Nanozymes offer several key advantages for ocular therapy, including potent antioxidant and anti-inflammatory effects, the capacity to inhibit angiogenesis, versatility within drug delivery systems, and strong stability and biocompatibility. These attributes underscore their unique value in ophthalmology. However, the path to clinical translation is not without its hurdles. Challenges such as ensuring long-term safety, achieving optimal targeting to specific ocular tissues, and simplifying complex preparation processes currently limit their widespread application. Addressing these limitations in future research is paramount. By continuously optimizing nanozyme synthesis, enhancing their stability, targeting specificity, and biocompatibility, conducting thorough investigations into their biological safety, developing novel nanozyme designs, and fostering strong multidisciplinary collaborations, nanozymes are poised to significantly advance ocular disease treatment, offering new strategies for

precise and personalized medicine in ophthalmology.

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