

Review

Ophthalmic Nanosystems with Antioxidants for the Prevention and Treatment of Eye Diseases

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Abstract: Oxidative stress may induce a series of pathophysiological modifications that are directly involved in the development of ophthalmic diseases like age-related cataract, macular degeneration or diabetic retinopathy, considered to be responsible for the majority of vision loss cases. Although various treatment options for eye diseases are available, multiple factors could limit their efficacy. Recently, the accelerated development of ophthalmic nanosystems has provided new possibilities for overcoming the limitations of existing ocular drug delivery methods. This review evaluates the current status of ophthalmic nanosystems loaded with antioxidants for the prevention and treatment of several eye diseases.

Keywords: nanosystems; antioxidants; ophthalmic administration

1. Introduction

Vision impairment is a major public health concern, affecting 2.2 billion people worldwide. According to a report from the World Health Organization (WHO), 65.2 million patients have a cataract and 3 million have diabetic retinopathy, diseases capable of producing a permanent vision loss [1]. A significant proportion of visually impaired patients are over 50 years old, where a constantly aging global population will likely further increase the incidence of severe eye diseases in the future [1]. The eye is an organ prone to oxidative stress due to high exposure to ultraviolet (UV) light. In addition, daily exposure to blue light (450–495 nm) from television, computer or mobile phone LED screens can also generate reactive oxygen species (ROS) in several eye structures [2–5]. Consequently, prolonged oxidative stress may induce a series of pathophysiological modifications such as lens protein precipitation or microvascular anomalies. These are directly involved in the development of ophthalmic diseases like age-related cataract or diabetic retinopathy [6,7]. Furthermore, photo-oxidative damage may contribute to retinal pigment epithelium degeneration, involved in the pathogenesis of age-related macular degeneration [8–11].

Although various treatment options for eye diseases are available, several factors could limit their availability and efficacy. Invasive treatment procedures of some ophthalmic pathologies, like classic surgery or laser therapy are usually too costly in developing countries and are often characterized by high recurrence rates of the disease [7]. Non-invasive treatments like topical drug administration are

widely used in ophthalmology, but their effectiveness is limited by the unique anatomy and physiology of the eye. The eye has structural barriers that can significantly reduce the ophthalmic bioavailability of the active substance [7]. Therefore, there is a pressing need to develop new strategies for drug delivery in the management of ocular diseases with the ultimate goal of reducing the incidence of vision loss and improving patients' quality of life.

In recent years, the development of nanotechnology has had a tremendous impact on multiple industrial sectors but also biomedical sciences. Nanocoating of biologically active substances gave them a superior capability of interacting with the organism at subcellular level, with improved specificity for designated molecular targets.

In ophthalmology, nanoformulations have provided new possibilities to overcome the limitations of existing ocular drug delivery methods. Various nanostructures like liposomes, nanospheres, or polymeric nanoparticles may successfully entrap the active substance, carrying it towards the internal structures of the eye that are usually difficult to reach using conventional drug formulations. Therefore, the inclusion of an ophthalmic drug in a nanostructure has the potential to improve the solubility, permeability, and stability of the active substance, with a clear augmentation of the ocular bioavailability [12].

Among various drugs used in ophthalmology, antioxidants are used for their capacity to scavenge free radicals and to prevent cellular and tissular damage caused by oxidative stress. Antioxidant substances may particularly benefit from being incorporated into nanosystems due to their poor pharmacokinetic properties and a clear propensity for rapid inactivation. Thus, a carefully chosen nanocarrier might protect the antioxidant drug from being prematurely degraded or removed by the eye's protective mechanisms. This process enhances the ocular bioavailability and possibly allows a more targeted effect towards specific eye components [7].

Although nanotechnology is increasingly used today for the development of intelligent systems that are capable of releasing active principles, few articles have focused on its ophthalmic applications. Therefore, this review aims to briefly present the state of the art regarding the development of ophthalmic nanosystems loaded with antioxidants designed to obtain superior therapeutical effects by improving the biopharmaceutical properties of the drug.

2. Methodology

A search was performed in the Web of Science, PubMed, and Scopus scientific databases, covering the last ten years (2009–2019). The search terms "nanoparticles/nanosystems," "antioxidant," and "ophthalmic/ocular" were used for data selection. Only full-text articles in English were included in this work.

3. Results and Discussion

3.1. Pharmacokinetic Aspects of Ophthalmic Drug Administration

Despite being an easily accessible organ, the eye poses significant challenges for effective drug administration. Anatomically, the human eye is divided into two sections: the anterior segment which includes the cornea, iris, lens, and aqueous humor; and the posterior segment which includes the vitreous body, retina, choroid, and the back of the sclera [12–14]. The systemic administration of drugs can deliver them to the anterior segment of the eye but with very low ocular bioavailability due to the presence of an anterior blood-aqueous barrier (BAB) formed by inner ciliary epithelia, endothelia around the iris, and ciliary muscle capillaries. To reach the posterior segment of the eye, a systemically administered drug would have to pass the posterior blood-retinal barrier (BRB) formed by the endothelia of the retinal capillaries and retinal pigment epithelium. The existence of two barriers, the BAB and BRB, can impair the passage of a systemically administered drug from the blood to the aqueous humor or the retina. Additionally, a systemically administered drug may suffer from first-pass metabolism, usually in the liver, or it can generate unwanted adverse effects at multiple levels.

Therefore, local (ophthalmic) administration of drugs is usually preferred, being more convenient and simpler [15].

To reach the anterior segment of the eye and to treat various ocular diseases like cataracts, dry eye syndrome, inflammatory conditions or glaucoma, a topically applied drug would have to pass the corneal barrier formed by five distinct layers: the epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The increased hydrophobicity of the epithelium coupled with the presence of tight junctional proteins between epithelial cells significantly limits the capacity of hydrophilic drugs to penetrate the cornea. Meanwhile, a more hydrophilic environment present in the stroma restricts the passage of lipophilic drugs. Given this extremely selective corneal barrier, topically applied ophthalmic drugs enter in the anterior segment of the eye after they are absorbed via the conjunctiva/sclera pathway. The pathway has a larger surface area and superior permeability compared to the cornea. Limiting factors that can impair the drug's capacity to access the inner segments of the eye include a possible elimination of the drug by conjunctival blood and lymphatic flow, as well as the size of the molecule rather than its lipophilicity. Moreover, the ophthalmic bioavailability of drugs is reduced further by other mechanisms such as metabolic degradation or a premature drug removal from the eye by tear clearance or nasolacrimal drainage [15,16].

Other alternative means to deliver the drug to the internal eye structures are intracameral or subconjunctival administrations, which allow access to the anterior segment of the eye. The other is intravitreal administration, which gives the drug the capacity to target retinal structures (Figure 1). The intracameral and subconjunctival routes of drug administration both avoid the cornea and BAB and have good efficacy due to the superior bioavailability of the active substance. Intravitreal administration allows a relatively good passage of the drug to the posterior eye structures, the vitreous being a more permeable barrier than the cornea. The main disadvantage of these alternative ocular routes is the discomfort and pain caused by the procedure itself, which can limit patient compliance [15,16].

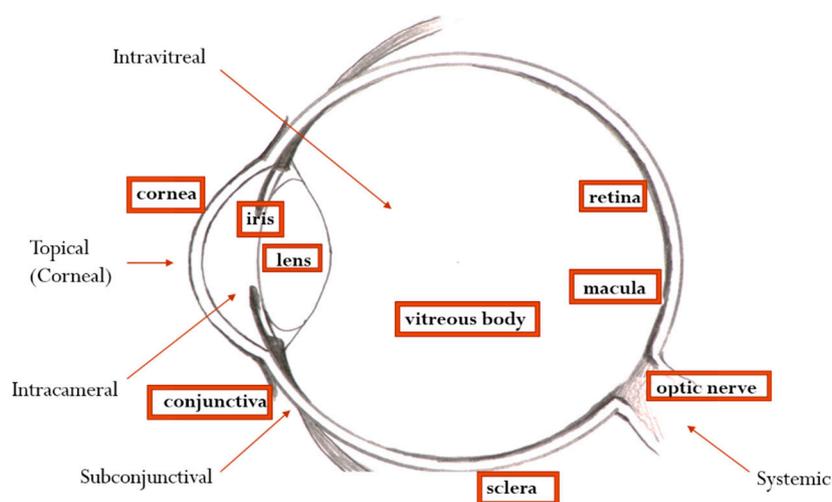


Figure 1. Main routes of ophthalmic drug administration.

3.2. State of the Art in the Formulation of Ophthalmic Nanosystems with Antioxidants

Designing a drug delivery system to target anatomical structures of the eye is a challenging process. In the last decade, the entrapment of the active substance in a nanosystem has become a promising solution for ocular diseases by improving ophthalmic bioavailability and favoring a constant concentration of the drug in the affected eye due to a prolonged-release, thereby ensuring a superior ocular tolerance. Nanosystems represent excellent reservoirs for the encapsulation of a variety of compounds and involve colloidal drug delivery systems, such as liposomes, micelles, niosomes, dendrimers, nanoparticles (NPs), implants, in situ hydrogels, or cyclodextrins (CD) [16]. Further, other innovative nanostructured drug-delivery systems have been developed. To reduce

mononuclear phagocyte system uptake and to extend biological activity of the incorporated substances, “stealth” liposomes have been synthesized with the inclusion of poly-(ethylene glycol) in liposome composition [17]. Another approach of delivering nucleic acids, small molecule therapeutic agents, quantum dots, or magnetic resonance imaging (MRI) contrast agents to their targets, involves incorporating them into cell-penetrating peptides [18]. Even a genome-editing tool like an endonuclease enzyme guided by a hybrid strand of ribonucleic acid (RNA) was incorporated successfully into nonviral vectors like cationic polymers or lipids for successful delivery to various cell types [19]. Additionally, poly-oxometalate nanoclusters have been successfully tested *in vivo*, protecting neurons against experimentally induced oxidative stress [20,21]. Moreover, recently published research highlighted the versatility of nanosystems (polymerosomes) in incorporating complex gaseous therapeutics like nitric oxide. This ability allows for smart, light-assisted delivery of the active substance in the treatment of ocular diseases like keratitis or corneal lesions [22–24].

The physico-chemical properties and drug-release characteristics of the nanosystems are influenced mainly by their composition (nature of polymer: natural or synthetic, molecular weight, polymer crystallinity, lipid type, presence of stabilizers), as well as the method of manufacture [25].

An optimal particle size to avoid local irritation and ensure an easy absorption by the corneal or conjunctival routes is considered to be less than 800 nm [26,27].

Among various drugs used in ophthalmology, antioxidants are particularly susceptible to denaturation and degradation during the manufacturing process. Natural antioxidant compounds such as baicalin, β -carotene, lycopene, epigallocatechine-3-gallate (EGCG), quercetin, curcumin, as well as metal oxides, are biologically active molecules with beneficial effects in a series of eye diseases. They often present low bioavailability that can be enhanced by chemical modification and/or pharmaceutical formulation [28].

The main characteristics of the studied antioxidant-loaded ophthalmic nanosystems are presented alphabetically in Table 1.

Baicalin was formulated as solid lipid nanoparticles (SLN) using the emulsification/ultrasonication method. The obtained SLN showed adequate physical characteristics and prolongation of baicalin release compared to the regular ophthalmic solutions [29]. Other solutions have been explored. In particular, vesicular nanosystems, such as liposomes, with optimal lipophilicity can improve drug permeation through the non-polar anatomical structures of the eye. They provide sustained drug release and allow good patient compliance by increasing the remanence time on the mucosa, thereby reducing the drug dose and frequency of adverse effects. Liposomes were shown to enhance the efficacy, stability, and solubility of drugs, which is a significant factor in the formulation of these systems being represented by choice of excipients, which must provide the transcorneal passage of drugs, but must also be compatible with the structures of the eye [30]. Baicalin vesicles were prepared using the thin film hydration technique. The vesicular systems showed a particle size greater than 600 nm and a negative charge. Liposomes exhibited the highest entrapment efficiency (EE) due to the lipophilicity of baicalin, which accumulated in the lipid layers of the multilamellar vesicles, as well as the presence of cholesterol which increased the hydrophobicity of the phospholipid layers [30].

Metal oxide nanoparticles have received particular attention in recent years due to their antiseptic, anti-inflammatory, and antioxidant properties. Given the increased toxicity of Ag and Au nanoparticles (NPs), the research has focused on cerium, a promising rare earth element. CeCl₃ loaded mesoporous silica (CeCl₃@mSiO₂) NPs for use in the prevention of cataractogenesis were prepared [31]. Cerium oxide nanoparticles (nanoceria) are antioxidants and possess catalytic activities that mimic those of biological antioxidants (superoxide dismutase, catalase). They also have great potential for use as drug carriers and delivery agents due to their attractive properties, i.e., biocompatibility and small particle size that allow for easier passage through cell membranes [32].

Coenzyme Q10-loaded liposomes coated with different concentrations of *N*-trimethyl chitosan, an excellent absorption enhancer, were prepared. The experimental results showed a deeper penetration of coated liposomes into the corneal epithelium in comparison to the non-coated ones [33].

Various biocompatible drug carriers have been incorporated to ensure optimal drug delivery formulations at the eye level and to increase effective drug concentration in the anterior or posterior eye tissue. Albumin is an attractive macromolecular carrier because of its non-immunogenic, non-toxic, biocompatible, and biodegradable characteristics, and it is being considered as a potent drug carrier to increase the solubility of poorly soluble compounds. Albumin-based nanoformulations (bovine serum albumin) loaded with curcumin, rosmarinic acid, and ursolic acid were prepared using the desolvation method. The results confirmed that the NPs had nanosized ranges, had increased drug solubility, and better stability after 2 months of storage both in a solution state and freeze-dried powder [34].

Another antioxidant, epigallocatechin gallate (EGCG), a polyphenolic compound known for its pleiotropic effects, was encapsulated in a nanosystem for protection against undesired environmental factors (light, moisture, oxygen) and to prolong its shelf life, to avoid degradation and provide a controlled release. Huang et al. reported the preparation of epigallocatechin gallate loaded NPs using the self-assembly method [35]. The polymer used in the preparation was gelatin, a preferred raw material due to its biodegradability and biocompatibility properties [36]. The synthesized NPs were decorated on the surface with hyaluronic acid to ensure prolonged retention on the eyes by increasing the adhesion of NPs to the mucus layer. The NPs showed an increase in particle size and a decrease in zeta potential proportional to the increase in hyaluronic acid concentration. The zeta potential was positive until it reached a 62.5 $\mu\text{g/mL}$ hyaluronic acid (HA) concentration, becoming negative at 125 $\mu\text{g/mL}$ HA. The NPs with a particle size of 253.4 \pm 7.3 nm and zeta potential of 9.2 \pm 1.8 mV (corresponding to a 62.5 $\mu\text{g/mL}$ HA concentration) showed a pH, osmolality, and refractive index similar to those of human tears. The NPs also demonstrated a high affinity for human corneal epithelium cells and anti-inflammatory effects after in vivo evaluation [35].

Table 1. Ophthalmic nanoformulations with antioxidants.

Nanosystem	Active Principle	Excipients	Characteristics			Reference
			Particle Size (nm)	Zeta Potential (mV)	Entrapment Efficiency (%)	
Solid lipid nanoparticles	Baicalin	Not available	91.42 \pm 1.02	-33.5 \pm (-1.28)	62.45% \pm 1.67%	Liu et al., 2011 [29]
Liposomes	Baicalin	PC Labrasol Cholesterol Bile salts Span 60	667.9 \pm 157	-16.8 \pm (-1.86)	>94%	Ashraf et al., 2018 [30]
Nanoparticles	CeCl ₃ @mSiO ₂	Mesoporous silica nanoparticles	87.6 \pm 8.9	-	7.35% \pm 4.33%	Yang et al., 2017 [31]
Nanoparticles	Cerium oxide (CeO ₂ , nanoceria)	Cerium nitrate hexahydrate	3–5	-	-	Kyosseva et al., 2015 [32]
Liposomes	CoQ ₁₀	N-trimethyl chitosan PC Cholesterol	63–78	8.83–24.5	>97%	Wang et al., 2011 [33]
Nanoparticles	Curcumin	Bovine serum albumin Glutaraldehyde	203.2 \pm 15.4	-17.04 \pm (-1.5)	>90%	Kim et al., 2019 [34]
Nanoparticles	EGCG	Gelatin HA	253.4 \pm 7.3	9.2 \pm 1.8	97.8% \pm 0.5% good tolerance	Huang et al., 2018 [35]
Lipid nanoparticles	EGCG	CTAB DDAB	<300	-	>90%	Fangueiro et al., 2014 [37]
Nanoparticles	EGCG	Gelatine HA RGD	168.87 \pm 22.5	19.7 \pm 2	up to 95%	Chang et al., 2017 [38]
Nanoparticles	Gold Resveratrol	Green synthetic method	20	-	-	Dong et al., 2019 [39]
Lipid nanocarriers combined with CD	Lutein	CD Tween 80 Span 60 Transcutol HP	336.8 \pm 43	-28	68.1% \pm 3.3%	Liu et al., 2014 [40]

Table 1. Cont.

Nanosystem	Active Principle	Excipients	Characteristics			Reference
			Particle Size (nm)	Zeta Potential (mV)	Entrapment Efficiency (%)	
Lipid nanocarriers	Lutein	Tween 80 Span 60 Transcutol HP	229.8.8 ± 65	−34.3 ± 0.2	59.0% ± 1.5%	Liu et al., 2014 [40]
Nanoparticles	Lutein	PLGA Tween 80 Poloxamer 407 Poly(ethyleneoxid)	222.9 ± 1.2	−32.4 ± 3.9	96.2% ± 2.7%	Bodoki et al., 2019 [41]
Nanoparticles	Resveratrol	Chitosan TPP PEG	–	129	91.89% ± 1.11%	Natesan et al., 2017 [42]
Nanoparticles	Resveratrol Quercetin	Chitosan TPP PEG	–	308	81.34% ± 3.21%	Natesan et al., 2017 [42]
Nanoparticles	Silver	<i>Tabernaemontana divaricata</i> extract	15–50	–	–	Anbukkarasi et al., 2017 [43]
Liposomes	α-tocopherol	PC Cholesterol Sodium hyaluronate	>1	–	–	Vicario-de-la-Torre et al., 2014 [44]
Nanoparticles	Ursolic acid	Bovine serum albumin Glutaraldehyde	234.7 ± 13.1	−11.66 ± (−1.1)	>90%	Kim et al., 2019 [34]
Liposomes	Vitamin A palmitate	N-trimethyl chitosan Poloxamer 407	<100	41.5–53.7	>84%	He et al., 2013 [45]
Nanoparticles	ZnO Galic acid coating on contact lenses	Chitosan	<40	–	–	Hoyo et al., 2019 [46]

Abbreviations: CD: β-cyclodextrins; CTAB: cetyltrimethylammonium bromide; DDAB: dimethyldioctadecylammonium bromide; EGCG: epigallocatechin-3-gallate; HA: hyaluronic acid; RGD: arginine-glycine-aspartic acid-peptide; NLCs: lipid nanocarriers; PC: phosphatidylcholine; SLN: solid lipid nanoparticles; PLGA: poly(lactic-co-glycolic acid).

Fangueiro et al. reported the development of lipid nanoparticles (LNs), an innovative vehicle for EGCG encapsulation, for use in the future treatment of several eye diseases (dry eye syndrome, age-related macular degeneration, glaucoma, diabetic retinopathy, and macular edema). LNs represent a new generation of drug delivery systems known as safe drug carriers due to their physiological lipid contents, which are biocompatible and biodegradable. The preparation was performed via the multiple emulsion method, using cationic lipids such as cetyl-trimethyl-ammonium (CTAB) bromide and dimethyl-diocta-decyl-ammonium bromide (DDAB) and a non-ionic surfactant (Poloxamer 188) as a stabilizing agent. Moreover, the cationic properties were exploited to provide the LNs with stability and to increase their mucoadhesivity on the eye surface by electrostatic attraction. The obtained particles were in the nanometer range (<300 nm), with good EE (<90%), and they revealed higher stability at 25 °C, as well as enhanced bioavailability and physiological compatibility with ocular tissue [37].

Chang et al. reported the obtention of EGCG loaded NPs using an arginine-glycine-aspartic acid peptide, with a hyaluronic acid–conjugated complex coating the gelatine. The obtained NPs had a mean diameter smaller than 200 nm, positive charge and good EE, for use in the treatment of neovascularization of the cornea [38].

The manufacture of metal nanoparticles using plant extracts or other biomolecules has become an attractive strategy that allows avoidance of any harmful reductant, rendering it useful in biology and medicine. Dong et al. reported on the fabrication of gold nanoparticles (AuNPs) through an eco-friendly method, using a herbal polyphenol (resveratrol) as both the stabilizing and reducing agents. The obtained AuNPs were spherical with a mean particle size of 20 nm [39].

A natural carotenoid pigment, lutein, was also incorporated in several nanosystems. Liu et al. combined lutein loaded lipid nanocarriers (NLCs) with 2% β-cyclodextrins (Table 1) using the hot sonication method and they obtained an increase of the EE and lower cytotoxicity in the bovine

cornea cells [40]. Bodoki et al. reported lutein loaded PLGA NPs preparation. The obtained NPs were incorporated in a bioadhesive thermosensitive gel based on Poloxamer 407 and polyethylene oxide. This process ensured a prolonged adherence to the mucosa after topical application in the eye. The combination of drug-loaded nanosystems with bioadhesive polymers can bring important benefits to the drug delivery system. Mucoadhesives attach to the mucin layer that covers the conjunctiva and the cornea, ensuring intimate contact between the drug and the biological tissues. This process results in a high local concentration of the drug, as well as its increased absorption through the biological membranes [41].

An interesting approach in the preparation of antioxidant-based pharmaceutical systems is the combination of several compounds with antioxidant action in the same formulation. Natesan et al. reported on the preparation of NPs loaded with resveratrol, alone or associated with quercetin, designed for the treatment of glaucoma. The NPs were prepared by the ionic gelation method, using chitosan and sodium tri-polyphosphate (TPP) as a polyanionic cross-linking agent. The NPs were modified with PEG (different molecular weights and in different concentrations). Spherical nanoparticles with a mean diameter greater than 100 nm were obtained. The association of quercetin in NPs with resveratrol increased the particle size and led to a decrease in the EE. It was observed that the increase of the concentration and molecular mass of the PEG caused the increase of the particle size and the decrease of the EE. This effect was probably because of reductions in the available space for the incorporation of the drugs. On the other hand, increasing the concentration of PEG leads to a decrease in the positive charge of the NPs (PEG and drugs can reduce the ionic interactions between the chitosan and cross-linking agent), thereby improving the biocompatibility and stability in the physiological fluids. Chitosan, being a cationic polyelectrolyte, can provide an improved residence of the preparation on the mucosa and, consequently, a prolonged release of the active principle. This is done by performing electrostatic interactions with the sialic acid residues in the mucus or with the negative charges on the surface of the epithelium [42].

Anbukkarasi et al. reported the successful green-synthesizing of silver NPs (AgNPs) using an ethanolic extract of the leaves of *Tabernaemontana divaricata*, intended for use in anticataractogenic potential [43].

Liposomes loaded with α -tocopherol were obtained to improve the stability and tolerability of vitamin E. The in vitro characterization revealed physiological values concerning pH, osmolality, and viscosity. The resuspension of liposomes in an isotonic solution of 0.2% sodium hyaluronate led to the best tolerance demonstrated in vivo after application by instillation [44].

Cationic liposomes based on chitosan were formulated to improve the ocular bioavailability of vitamin A by increasing retention time in the eye. Vitamin A-loaded obtained liposomes were then dispersed in an in-situ gel-forming matrix, consisting of Poloxamer 407 25%. Studies have shown that colloidal dispersions did not influence the gelation temperature, and by dispersing them in the in situ forming gel, a delayed release of the drug and an increased corneal retention time were obtained [45].

An interesting strategy aimed at the reduction of adverse reactions (keratitis, acute red eye) and discomfort caused by the use of contact lenses is based on coating the contact lenses with metal-oxide nanoparticles and functionalization of the surface with hydrophilic polymers. Hoyo et al. reported the simultaneous depositing of an aqueous suspension containing ZnO nanoparticles (antibacterial activity by formation of reactive oxygen species that affect bacterial membrane), chitosan (natural polymer known for biocompatibility, biodegradability, wettability, and antibacterial properties), and gallic acid (antioxidant activity) in a one-step sonochemical coating process. The ternary hybrid coating improved the surface wettability and antioxidant activity by 95% and showed high antibacterial efficiency [46].

3.3. Preclinical In Vivo and Ex-Vivo Studies with Ophthalmic Nanosystems with Antioxidants

This review of published data showed that ocular nanosystems with antioxidants presented significant protective effects against multiple ocular pathologies, demonstrated in specific in vivo or ex-vivo animal models. The studies by Li et al. [47], Bodoki et al. [41], and Anbukkarasi et al. [43] used

the selenite-induced cataract model in rodents, obtaining a reduction of the disease progression under treatment with nano entrapped antioxidants like baicalin, lutein, or silver. In this model, the antioxidant molecules protected the lens against oxidative damage caused by a toxic substance-sodium selenite. Several in vivo studies evaluated the protective effect of nanoceria against light-induced retinal damage or in genetically modified animals like tubby mice or Vldr knockout mice. It demonstrated good effects in preventing retinal degeneration by a scavenging effect of ROS and a reduction of MAP kinase activity in the retina [48–50]. Kyosseva et al. [51] also found that the protective effect of nanoceria against retinal lesions is due to the inhibition of some pro-angiogenic factors. Huang et al. [35] proved that an ophthalmic nanosystem with an epigallocatechin gallate might alleviate the dry eye syndrome in rabbits through antioxidant and anti-inflammatory mechanisms. Furthermore, Natesan et al. [42] found that nano entrapped resveratrol can reduce intraocular pressure in rabbits.

Although preclinical data concerning the ophthalmic effects of antioxidants encapsulated in nanosystems are very promising, further research is necessary to ascertain if these results can be translated into human medicine. The antioxidant-loaded ophthalmic nanosystems are presented alphabetically, the main findings of the studies were also presented, alongside the route of administration and the applied doses (Table 2).

Table 2. In vivo and ex-vivo studies using ophthalmic nanosystems with antioxidants.

Type of Formulation/Mode of Administration/Dose	Experimental Model	Findings	Reference
Baicalin: Solid lipid nanoparticles with baicalin/Corneal/20 μ L	Selenite induced cataract in rat pups	Reduction of cataract onset and progression	Li et al., 2018 [47]
Cerium: Solid nanoparticles (5 nm) with CeO ₂ /Intravitreal/0.1–1 μ M	Light-induced photoreceptor degeneration in albino rats	In vivo protection of photoreceptor cells by radical-scavenging mechanism	Chen et al., 2006 [48]
Solid nanoparticles (3–5 nm) with CeO ₂ /Intravitreal/1 μ M	Tubby (<i>tub/tub</i>) mutant mouse model	Protection of retinal structure and function by up-regulation of genes associated with antioxidant defenses	Cai et al., 2012 [49]
Solid nanoparticles (3–5 nm) with CeO ₂ /intravitreal/1 mM	Vldr knockout mouse model	Inhibition of retinal lesions by reduction of ROS and VEGF levels	Zhou et al., 2012 [50]
Solid nanoparticles (3–5 nm) with CeO ₂ /Intravitreal/1 mM	Vldr knockout mouse model	Inhibition of retinal pro-inflammatory cytokines and pro-angiogenic factors	Kyosseva et al., 2013 [51]
Curcumin: Nanoparticles (100 nm) with curcumin	Ex-vivo oxidative stress on rabbit cornea and retina	Reduction of reactive oxygen species (ROS) in rabbit retina	Kim et al., 2019 [34]
Epigallocatechin gallate : Solid nanoparticles (250 nm) of epigallocatechin gallate/Corneal/20 μ L	Dry eye syndrome (DES) rabbit model	Normalization of corneal architecture, inhibition of inflammatory cytokine production	Huang et al., 2018 [35]
Lutein: PLGA nanoparticles (222.9 nm) with lutein/Corneal/1278 μ g/mL	Selenite induced cataract in rat pups	Reduction of cataract onset and progression	Bodoki et al., 2019 [41]
Resveratrol: Chitosan nanoparticles (100 nm) with resveratrol/Corneal/50 μ L	Normotensive eye rabbit model	Reduction of intraocular pressure	Natesan et al., 2017 [42]
Silver: Silver nanoparticles (15–50 nm)	Ex-vivo model of selenite-induced cataract in rats	Reduction of cataract onset and progression	Anbukkarasi et al., 2017 [43]

3.4. Mechanisms of Action of Antioxidants Entrapped in Nanosystems with Ophthalmic Application

An antioxidant is a molecule that can significantly decrease the oxidation of specific substrates (proteins, lipids, DNA), thereby reducing the destructive cellular consequences of oxidative stress [7]. Extensive research has demonstrated that highly reactive oxygen species like the superoxide anion radical, hydrogen peroxide, or hydroxyl radical, are generated in the intracellular environment under certain conditions and may cause significant cellular damage. They are involved in the pathogenesis of a variety of diseases, including cardiovascular disorders, chronic inflammation, diabetes, or neurodegenerative disorders. In ophthalmology, they are linked to a series of conditions like cataract, macular degeneration, or retinopathy, making them attractive pharmacological targets. Therefore,

antioxidant molecules capable of correcting the oxidative stress imbalance are becoming increasingly crucial to the prevention and treatment of various eye diseases [7]. Although important information regarding the molecular mechanisms of action of antioxidants has emerged from experimental studies, further research is necessary to clarify their complex biological effects (Figure 2).

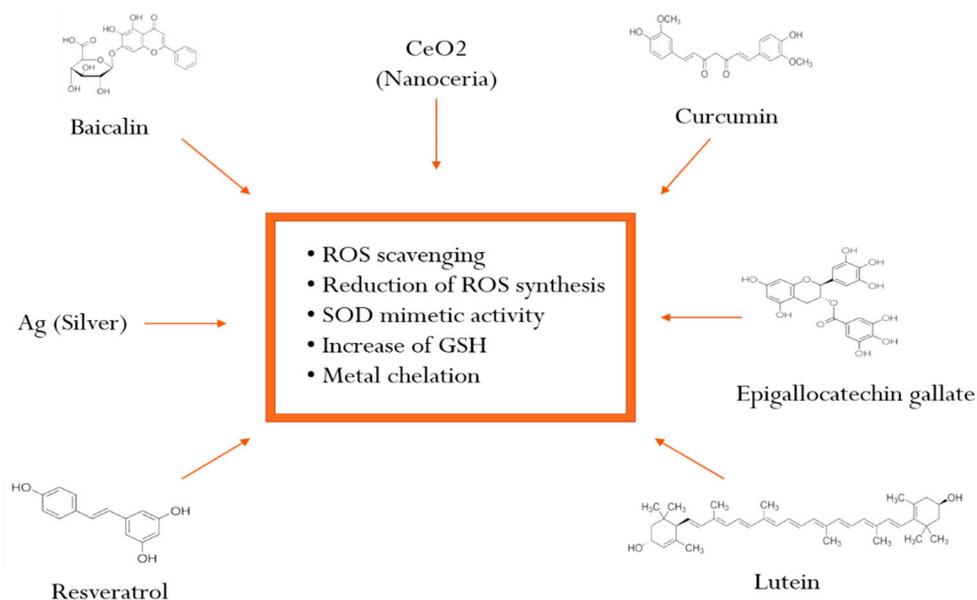


Figure 2. Mechanisms of action of antioxidants entrapped in ophthalmic nanosystems (Abbreviations: ROS: reactive oxygen species; SOD: superoxide dismutase; GSH: glutathione).

3.4.1. Baicalin

Baicalin is a flavonoid from the plant species *Scutellaria baicalensis*, a herbal remedy used for millennia in traditional Chinese medicine. A recent study showed significant antioxidant and anti-inflammatory properties of baicalin but also consistent antiviral effects [52]. In a recent study, solid lipid nanoparticles with baicalin proved to be an effective ROS scavenger by augmenting superoxide dismutase (SOD) activity, as well as the level of glutathione [47].

3.4.2. Cerium

Cerium is a rare earth element that can exist both in +3 and +4 oxidation states, with important antioxidant enzyme-mimetic activity, as well as ROS and RNS scavenging capability, especially in its nanoparticulated form, nanoceria. The scavenging properties of nanoceria are augmented if the size of the nanoparticles decreases, with the smaller particles being extremely reactive. The unique chemical, biological, and surface properties of nanoceria make them essential in several economic sectors like metallurgy or the oil industry, but they are also attractive for a variety of biomedical applications including ophthalmology [53].

Korsvik et al. [54] demonstrated the SOD-mimetic activity of nanoceria synthesized with a higher Ce³⁺/Ce⁴⁺ surface ratio which favored the catalytic degradation of superoxide anion. Further, Rzigalinski et al. [55] showed catalase (CAT)-mimetic activity due to the regenerative nature of the Ce³⁺/Ce⁴⁺ redox couple on the nanoparticle surface.

In addition, several studies demonstrated a significant reduction of nitrosative stress both in vitro and in vivo. Xue et al. [56] proved that nanoceria could effectively scavenge hydroxyl radicals in vitro more effectively at higher Ce³⁺/Ce⁴⁺ surface ratios. Meanwhile, Zhang et al. [57] and Dowding et al. [58] showed a protective effect against the damage of cellular structures caused by aggressive free radicals ·OH and ·NO.

3.4.3. Curcumin

Curcumin is a water-insoluble pigment extracted from *Curcuma longa* (turmeric), a plant species extensively used as a spice in South-East Asia. In recent years, extensive research confirmed that curcumin could downregulate genes involved in uncontrolled cellular proliferation by inhibiting nuclear factor Kappa B (NF- κ B) activation. In addition, curcumin reduces the synthesis of free radicals; therefore, it has antioxidant properties. In ophthalmology, curcumin showed beneficial effects in dry eye syndrome and some forms of retinopathy due to its inhibition of interleukin (IL)-1 beta production and c-Jun N-terminal kinase (JNK) activation [59].

In another study, curcumin was able to reduce the progression of retinopathy in diabetic mice treated with streptozotocin by inhibiting the expression of vascular endothelial growth factor (VEGF). The anti-angiogenic properties of curcumin could be useful not only in retinopathies but also in age-related macular degeneration [60].

3.4.4. Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (EGCG) is the most abundant and potent catechin of green tea. Chemically, it is a polyphenolic compound that is able to successfully scavenge reactive oxygen species (ROS) due to the presence of the galloyl group on the B and D rings. It inactivates superoxide anion via a reaction leading to the oxidation of the D ring. EGCG may also inhibit lipid peroxidation and damage to ATPases, but it can also decrease the formation of hydrogen peroxide and damage to DNA caused by UVB irradiation [61].

EGCG can also indirectly act as an antioxidant by increasing the level of phase II antioxidant enzymes like superoxide dismutase or glutathione peroxidase. New research claims that it can interact with signal transduction pathways and transcription factors, which can explain its complex effects [62].

3.4.5. Lutein

Lutein is a natural carotenoid pigment, uniquely concentrated in the lens where it can reduce the photochemical and oxidative damage by filtering high-energy UV light and by scavenging reactive oxygen species. Therefore, it has a potential role in the prevention of cataract [63].

Several in vitro studies have shown that in addition to quenching reactive oxygen species directly, lutein may prevent protein, lipid, or DNA from suffering oxidative damage. Several mechanisms are responsible for the protection against oxidative damage, including reduction of the level of H₂O₂-induced protein carbonyl and MDA, increase in the level of GSH, and an increase of the GSH:GSSG ratio [64].

In animal models of selenite and diabetes-induced cataract, lutein managed to slow down the cataract development, due to its capacity to inhibit lipid peroxidation [41,65]. In humans, a recently published meta-analysis demonstrated that increased blood concentrations of lutein and zeaxanthin might be associated with the reduced risk of nuclear cataract, but the efficacy is reduced by their low systemic bioavailability [66].

3.4.6. Resveratrol

Resveratrol is a natural polyphenolic compound present in a variety of plant species, especially in some grape varieties. Several studies have confirmed the anti-inflammatory, antitumoral, antiviral, and neuroprotective effects of this molecule. In addition, it is a powerful antioxidant that acts as an ROS scavenger but also as a metal chelator. Resveratrol can neutralize hydroxyl and hydroperoxyl radicals and can protect the cells against oxidative stress and prolong their survival. Moreover, indirect antioxidant effects are presumed for this compound by the modulation of cellular antioxidant pathways [67].

3.4.7. Silver

Silver ions are often used for medical purposes due to their antibacterial and immunomodulatory effects. Silver disrupts multiple bacterial processes, including disulfide bond formation and iron homeostasis. It can also expand the antibacterial spectrum of existing antibiotics [68]. In recent years, silver nanoparticles synthesized using vegetal extract proved to be powerful antioxidants. Das et al. demonstrated the clear ROS scavenging potential for silver nanoparticles synthesized with an extract from *Ananas comosus* but also nitric oxide scavenging activity [69].

4. Conclusions

Recently, there has been growing interest in the development of nanosystems loaded with antioxidants for ophthalmic use. Several nanosystems have been studied preclinically in vivo, with good results, and the properties of the formulations have been optimized to achieve some significant characteristics required by the ophthalmic tissues. The characteristics include pH, osmolality, and viscosity. Further development of the technology is still necessary to obtain safe, economical, and reproducible antioxidant-loaded nanosystems, capable of preventing or treating ophthalmic diseases.

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