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Review

Nanomedicine: Pioneering a New Frontier in Neuro-Ophthalmology

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Abstract

Nanotechnology is one of the most promising fields of study, and it represents a pioneering leap in science and technology by the precise control over materials at the atomic and molecular level. This transformation affects numerous aspects of modern human life, including medicine, healthcare, electronics, computing, and energy storage. Nanotechnology has shown significant advancements in managing various health problems through different nano-formulations. These engineered nano-systems can be used as drug delivery vehicles, gene therapy vectors, imaging agents, etc. A range of neuro-visual disorders have been identified through the years and found to be associated with malfunctioning the eyes and the nervous system. State-of-the-art nano-formulations are currently being examined for their possible beneficial effects in diagnosing and treating various nervous-related ocular conditions. Nano-emulsions and polymeric hydrogels are efficient drug delivery vehicles of anti-glaucoma drugs. Superparamagnetic nanoparticles (NPs) are extensively being used as magnetic tags for the non-invasive imaging of transplanted cells in patients with optic neuritis and bio-engineered sensors are utilized in neuromyelitis optica diagnosis, though the colorimetric detection of anti-aquaporin-4 antibodies by silver NPs. These are just a few of the

most recent advancements in neuro-ophthalmology. This review summarizes the central neuro-ophthalmologic disorders affecting the global healthcare system, emphasizing the utilization of revolutionized nanomedicine-based tools for managing these conditions. Addressing the potential challenges and side effects is critical for the safe and effective integration of nanotechnology in various fields of study, especially in healthcare.

Keywords
Neuro-ophthalmology; nanomedicine; glaucoma; optic neuritis; neuromyelitis optica; ischemic optic neuropathy

1. Introduction

Nowadays, nanotechnology is one of the most promising fields of study, and it bridges the gap between science and technology. It contributes to developing more effective and sustainable energy sources, cutting-edge electronic devices, and medical breakthroughs [1]. Interestingly, the flourishing global nanotechnology market exceeded $125 billion by 2024 and is persistently receiving governmental and private funding [2].

More specifically, it can be used to treat contaminated water through the ability of Nano-ZnO to absorb ultraviolet-visible light [3]. Various metals, metal oxides, and semiconductor nanostructures can be used as nano-catalysts for multiple applications like energy-saving processes to fulfil human needs. In the food industry, nanotechnology supports the quality and quantity of food, secures food safety and facilitates food packaging [4]. For example, poly (vinyl alcohol) (PVOH) based films are widely used in the food industry due to their easy film-forming ability [5]. This field of study is extensively used in the pharmaceutical and medical fields due to the nano systems' unique pharmacokinetic and pharmacodynamic profile. Several examples are the utilization of titanium NPs for manufacturing anti-UV radiation creams, the development of pharmaceutical drug delivery release systems, or the assembly of nano-based biosensors for the traceability of pathogenic bacteria [4]. The outstanding physical properties of these state-of-the-art nanostructures enhanced the utilization of nanotechnology in various fields of modern human life, including the prevention, diagnosis and treatment of different neuro-ophthalmological conditions.

To start with, the human eye is a complicated organ with very well-established visual perception. It is separated into two main parts, anterior and posterior [6]. As illustrated in Figure 1, the anterior segment of the eye consists of the conjunctiva, cornea, sclera, uveal tract, aqueous humor, and lens, representing one-third of the structure. These parts of the eyes are primarily accessible through topical eye drops, ointments, or gels. The posterior segment of the eye consists of the inner part of the choroid, vitreous chamber, retina, and, of course, the optic nerves, representing two-thirds of the structure [7]. The retinal cells receive the light from the lenses, translate it into electrical signals, and transfer it to the brain through the optic nerves. The signaling stimuli are then transferred to the brain cortex through the optical tracts, enabling the processing of the visual information from the brain [8]. These parts of the eye are mainly accessible through intravenous and intravitreal injections. Despite the remarkable structural variability, each segment of the ocular structure is highly complicated and exhibits difficulties that may influence the diagnosis and treatment of a

condition [7]. The various ocular barriers (e.g., corneal, aqueous, inner, and outer blood-retinal barrier) isolate the eyes from the rest of the body, protecting the organs from the external environment and systemic circulation [9, 10]. The presence of these protective barriers minimizes the permeability of different drugs to the patient's eye, limiting their subsequent effectiveness [10]. Consequently, higher drug doses are commonly being used, raising concerns regarding toxicity issues and off-target side effects [11].

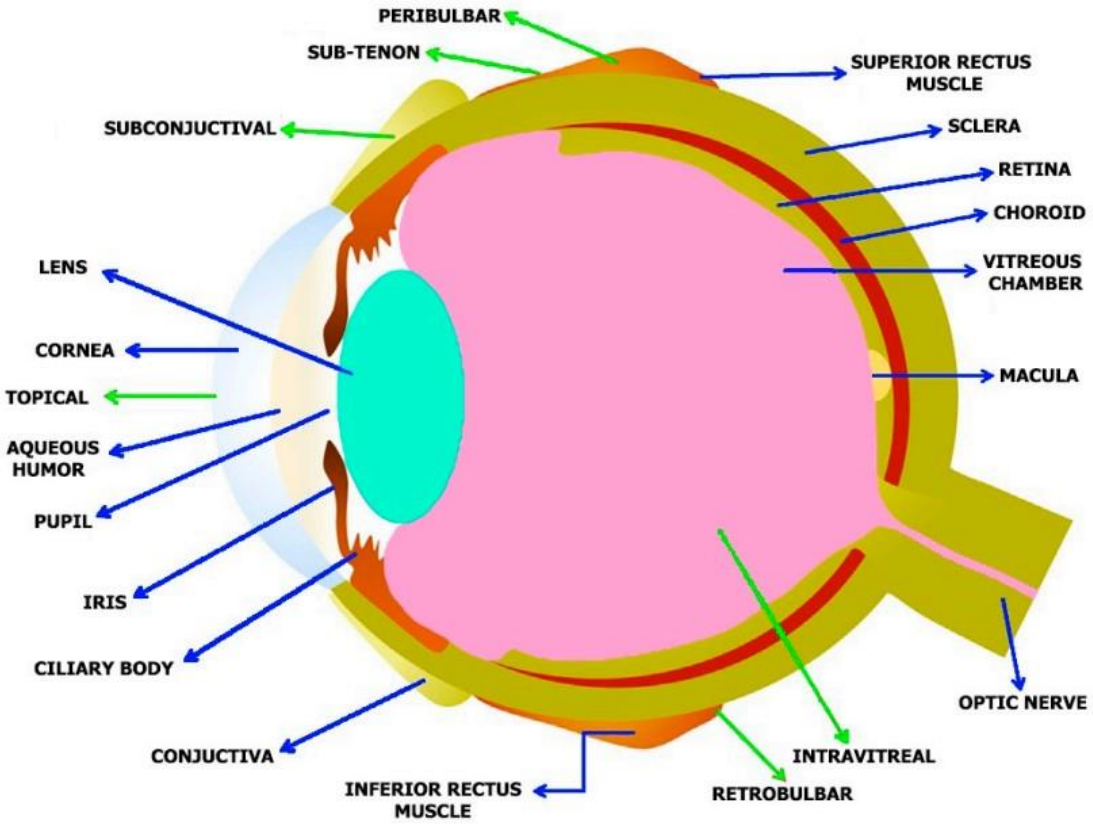

Figure 1 Graphical representation of the human eye and administration routes for both nano-based and traditional medicines. The blue arrows designate the different ocular parts, and the green arrows designate the possible administration routes [6].

Various scientists support that the eyes reflect the health status of the nervous system, indicating the possible changes that may be caused during disease progression [12]. A range of neurologic and neurodegenerative conditions deregulate the visual system, requiring multiple neuro-ophthalmic tests for the correct diagnosis of the condition [13]. Nowadays, the interdisciplinary concept of neuro-ophthalmology bridges the fields of neurology and ophthalmology. It is a highly dynamic and emerging field of science that focuses on diagnosing and treating nerve-related ocular conditions [14].

The earliest impact of this subfield area of study involved the formulation of novel pharmaceutical compounds, implantable biomaterials, and nanodevices, as well as the development of new diagnostic modalities [15]. These state-of-the-art nano-formulations are currently being examined for their possible beneficial effects in diagnosing and treating various nervous-related ocular conditions such as glaucoma, optic neuritis, neuromyelitis optica etc.

First, different types of NPs are being examined for their beneficial effect on medical diagnosis. For example, the development of silver selenide NPs encapsulated in an arabinogalactan polymeric matrix has been discussed for their possible utilization as fluorescent dyes in photothermal therapy. A study by *Titov EA et al.* highlighted their non-toxic effects on the cerebral cortex, which is responsible for essential physiological functions such as eye movement and visual stability [16]. Additionally, novel upconversion nanoparticles (UCNPs) showed promising results for managing various life-threatening disorders [17]. These nanostructures mediate the conversion of near-infrared (NIR) light to ultraviolet (UV) or visible (Vis) light, enabling deeper tissue penetration with limited neuronal damage and toxicity [18]. In photothermal therapy, UCNPs trigger the production of radicals near the tumour microenvironment, boosting cellular apoptosis. These newly introduced nanostructures are an important breakthrough for biomedical engineering, imaging, and drug delivery applications. They can be used to manage many other conditions, including ocular abnormalities [19]. In terms of disease treatment, bio-engineered nanoceria are being used to treat oxidative conditions like age-related macular degeneration (AMD) and colloidal NPs can facilitate drug delivery applications for managing chronic diseases like glaucoma. Another interesting example is using non-invasive intraocular monitoring devices, such as the IOP, for different biophysical measurements through nanotechnology-based biosensors. Finally, nanomedicine can be used in theranostics, coupling disease diagnosis, and treatment all at once [15].

As mentioned earlier, nanomaterials can bypass the different ocular barriers, travel along the optic nerves and reach the affected regions of the brain (Figure 2). This precise delivery systems can be crucial for the management of different ocular neurologic disorders. This review summarizes the main neuro-ophthalmologic disorders that currently affect the global healthcare system, giving special emphasis to the utilization of revolutionized nanomedicine-based tools for managing these conditions.

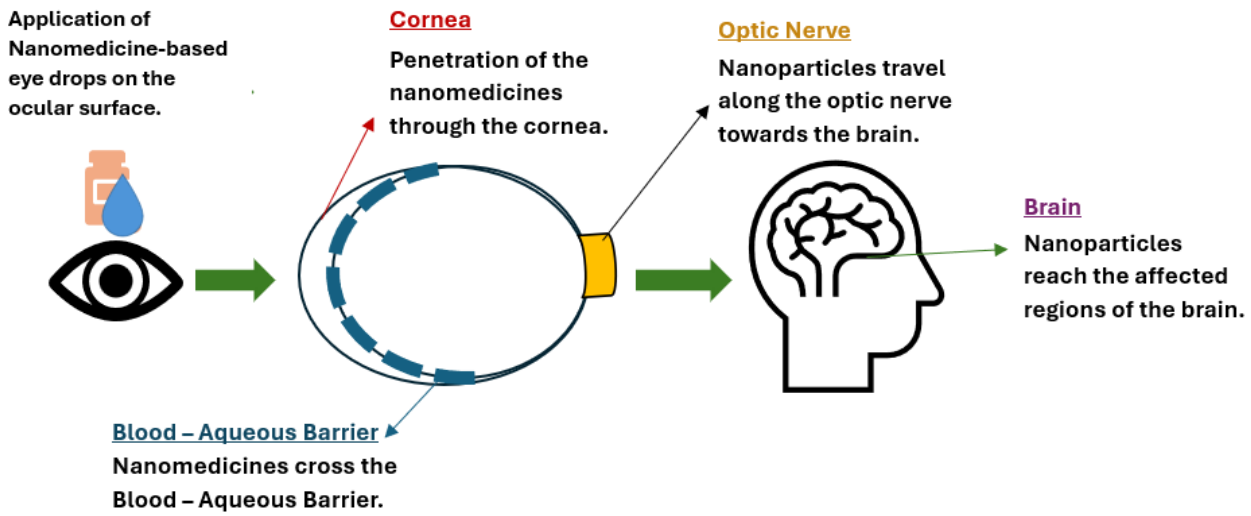

Figure 2 Schematic representation of the Nanomedicine effect mechanism for managing different neuro-ophthalmological conditions.

2. Nano-Formulations in Neuro-Ophthalmology

Nano-formulations have been extensively studied for their possible utilization in diagnosing and treating neuro-ophthalmological diseases due to their unique physicochemical characteristics and their variability in structure and composition. The two major nanomaterials currently used are organic, such as lipid-based nanoparticles, dendrimers, polymeric nanoparticles, and micelles. Natural biopolymers and inorganic nanomaterials include metal-based nanoparticles, Quantum Dots (QDs), carbon nanotubes, and mesoporous silica nanoparticles [20-23].

These nano-formulations exhibit unique physicochemical characteristics including size, surface charge, hydrophilicity or hydrophobicity and biodegradability that are highly associated with the bioavailability, biodistribution, absorption and elimination of the nanodrugs. Starting with the size, the cellular uptake of these nano-formulations is a size-dependent process and affords better internalization of smaller particles rather than larger ones. Upon intraocular administration, nanostructures can bypass the eyes' complex physiological barriers and evenly distribute them in their target cells. In contrast, upon systemic or topical administration, smaller-sized nanostructures are rapidly eliminated by circulation, while particles larger than 100 nm could remain in the neuro-ocular tissues, sustaining drug release. Their surface charge modulates the endocytosis, the penetration, and the biodistribution of the system. Various studies have shown that positively charged cationic nano-formulations exhibit maximum levels of targeted cellular uptake due to their biological interactions with the anionic, negatively charged intercellular components. Hydrophilic, lipophilic, or amphiphilic nanocarriers exhibit better permeability, bioavailability, cellular endocytosis, and diffusion within the various neuro-ophthalmic components like the cornea and sclera, triggering better cellular internalization and bioavailability. Another important aspect is the biodegradability of these nano-systems, which is highly dependent on the composition, the molecular weight, and the route of administration within the organism [20].

Biodegradable materials, like PLGA and PLA, have been extensively used due to their biocompatibility, safety, and efficacy in multiple drug delivery applications [24]. The field of nanotechnology has undergone enormous growth based on how these physicochemical characteristics modulate the “nano-bio” interactions, boosting the development of advanced diagnostic and therapeutic tools [20]

3. Different Neuro-Ophthalmological Manifestations and the Contribution of Nanomedicine

Nowadays, optic nerve disorders are a major cause of morbidity worldwide. Glaucoma, Optic Neuritis, and Ischemic Optic Disorder [25]. Specifically, the optic nerve is a white-matter tract that carries information from the eyes to the human brain for further processing. Upon optic nerve damage, the brain stops receiving visual information correctly, obscuring the eyesight [26].

3.1 Glaucoma

Glaucoma is the second leading cause of blindness worldwide, and the number of patients will reach 111.8 million by 2040 [27, 28]. Most of the time, both eyes are affected by the build-up of aqueous humor, causing an abnormal increase in intra-ocular pressure (IOP) [29]. Despite the elevated levels of IOP, this condition is also associated with other manifestations like atrophy of the

optic nerve, degeneration of the retinal ganglion cells (RGC), degeneration of oligodendrocytes and insidious problems in the peripheral vision [25].

3.1.1 Challenges in the Treatment of Glaucoma

All current antiglaucoma medications generally focus on lowering the IOP to manage vision loss [28]. Topical drug therapies, such as glaucoma eye drops, are mainly used to manage the disease due to their non-invasive administration to the ocular surface and anterior eye segment. Their limited production costs and their ease of use make them a principal choice for doctors [27]. These antiglaucoma drugs are mainly used to reduce the IOP by facilitating the outflow of aqueous humour or by decreasing its production of. Unfortunately, eye drops come with several drawbacks, such as insufficient drug delivery to the patient's eye, poor patient compliance due to the need for regular administrations, and tolerance development over time. All these minimize the effectiveness of the therapy and maximise the risk of disease progression [19].

As previously mentioned, eye drops are the commonest treatment option for managing the condition. There are multiple types of anti-glaucoma eye drops; therefore, choosing the correct medication depends on several parameters, including glaucoma type, severity and the patient's general medical image. If the selected medication fails to fulfill the patient's needs, another medication type is selected. The main types of anti-glaucoma eye drops are prostaglandin analogs (e.g. bimatoprost, latanoprost, tafluprost, travaprost), beta blockers (betaxolol and timolol maleate), carbonic anhydrase inhibitors (brinzolamide, dorzolamide) which are commonly prescribed as part of a combination therapy as well as alpha agonists (brimonidine tartrate and apraclonidine) which are mainly used as a combination therapy due to their extensive side-effects. A newer medication category is the Rho-kinase inhibitors (Rocklatan and Rhopressa), which are frequently prescribed with prostaglandins due to their supplemental modes of action. Other medication combinations include alpha agonists with beta-blockers, carbonic anhydrase inhibitors with beta-blockers, and carbonic anhydrase inhibitors with alpha agonists [30]. The table below (Table 1) summarizes the main types of anti-glaucoma eyedrops, their principal mechanisms of action, and their possible clinical side effects.

Table 1 Main categories of anti-glaucoma drugs.

Anti-glaucoma eyedrops	Mode-of-action	Side-effects
Beta blockers (e.g. Timolol maleate) [31]	Decrease the production of aqueous humor [31].	Ocular irritation, dryness, itchiness, and browache [32]. May cause cardiovascular and respiratory side effects to patients with contraindications to beta-blockers [33].
Cholinergics (e.g. Citicoline) [34]	Decrease ocular pressure. Improve glaucomatous impairment, limit neurodegeneration by reducing glutamate excitotoxicity and oxidative stress, increase neurotrophin levels,	Relatively free of side effects. Sometimes may cause mild digestive problems [34].

	ameliorate mitochondrial function and restores membrane integrity [34].	
Prostaglandin analogs (E.g. Latanoprost) [31]	Decrease IOP by elevating uveoscleral outflow [31].	Sometimes may cause hypertrichosis, melanogenesis, hyperpigmentation of eyelids and iris, conjunctival hyperemia and uveitis [35].
Rho-kinase inhibitors (Rhopressa) [36]	Enhance aqueous humor outflow through cytoskeletal changes. Decreasing IOP [36].	Sometimes may trigger conjunctival hyperemia [36].

As it was previously mentioned, some patients may develop tolerance to their treatment plan. In this case, alternative therapeutic procedures can be used like laser surgery, medical device implantation and incisional surgery. However surgical interventions are invasive, expensive, and sometimes inefficient [37]. Additionally, the metabolic, static, and dynamic barriers of the eyes minimising local drug delivery. Starting with the static barriers, the conjunctiva, sclera, and cornea exhibit variability in the polarity, hydrophilicity, and change, blocking drug passage. On the other hand, dynamic barriers are the quick removal of the eyedrops through the conjunctival veins and nasolacrimal drainage. Drugs can also be rendered inactive by ocular metabolic enzymes [27].

3.1.2 Nanomedicine-Based Treatment of Glaucoma

To overcome any limitations associated with the treatment of glaucoma, nanotechnology-based interventions would be useful in improving drug bioavailability, monitoring drug release, and minimizing the possible side effects that arise after glaucoma drug administration [6]. As shown in Figure 3, microscale and nanoscale formulations, including nanoparticles, liposomes, and micelles, can maximize drug bioavailability, solubility, and shelf life [28].

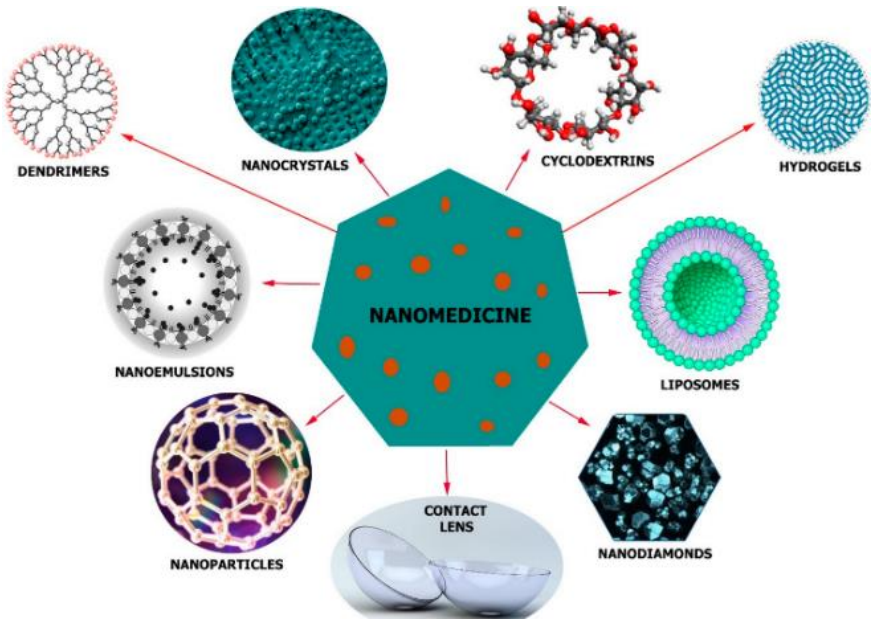

Figure 3 Graphical representation of the different nanotechnology-based approaches currently being studied for treating Glaucoma [23].

Starting with the nanoparticles are ideal solutions for drug delivery applications due to their ability to bypass biological barriers effectively. Nano-emulsions (NEs) exhibit high levels of drug solubility, and nanodiamonds are ideal for surface functionalization and, thus, targeted delivery. Hydrogel and nanocrystal complexes can be used to deliver various water-soluble drugs, while dendrimers and liposomes can transport a range of hydrophobic and hydrophilic drugs. Lastly, contact lenses are capable enzyme-triggered release, and nano-cyclodextrins can form inclusions to transfer lipophilic drugs without altering their molecular build-up [6].

In general, various authors have proposed using hydrogels to treat glaucoma; however, when these drug delivery systems are combined with nanoscale particles, a more targeted drug delivery approach can be achieved [27].

Hydrogels are the principal constituent of contact lenses (CL), and due to their remarkable affordability and biocompatibility, CL has attracted the attention of the scientific community as a means of delivering ocular medications [38]. CL can be used to treat a range of ocular conditions like glaucoma, especially due to their close contact with the cornea. The most important types of CL are made up of hydroxyethyl methacrylate (HEMA), Methacrylic acid (MAA), poly (vinyl alcohol) (PVA), and N-vinyl-2-pyrrolidone (NVP), Poly (2-hydroxyethyl methacrylate) (pHEMA). Several authors support that soaking commercially available CLs in a solution of timolol-propoxylated Glyceryl Triacylate (PGT) nanoparticles or timolol- Ethylene Glycol Dimethacrylate (EGDMA) nanoparticles promote a prolonged drug release [27].

In 2019, Sekar et al. proposed that polymeric hydrogels loaded with Vitamin-E triggered a sustained release of the glaucoma drugs bimatoprost and latanoprost [39]. A few years later, a study by Maulvi et al. exhibited that silicone hydrogel CLs loaded with graphene oxide (GO) improved Bimatoprost release. Specifically, GO molecules trigger an increase in the number of hydroxyl and carboxylic groups, improving the water retention of the CLs and, as a result, the swelling, transmittance properties and biocompatibility properties of the lenses [38]. In the same year, a study carried out by the National Taiwan University of Science and Technology, examined the therapeutic efficacy of the dual-drug delivery system made up of latanoprost-loaded hydrogel and curcumin-loaded nanoparticles, under oxidative stress conditions. In fact, the long-term use of latanoprost, may be responsible for the development of oxidative stress, thus, the possible therapeutic efficacy of the system was assessed in-vitro using human trabecular meshwork (TM) cells. Very promising results were obtained from the in-vitro experiments, exhibiting a drastic decrease in oxidative stress-mediated damage in the cultured cells. Similar results were obtained from in-vivo experiments on rabbits, underlying curcumin's antioxidant properties and the system's therapeutic efficacy [40]. Finally, a year later, in 2020, J. Jeremy Chae and his team utilized a microneedle to inject an in situ-forming hyaluronic acid (HA) hydrogel to stretch the suprachoroidal space (SCS) of the model animal eye. This enlargement boosted the outflow of aqueous humor and finally reduced the IOP levels. This non-surgical and drug-free approach would be an ideal solution for the treatment of ocular hypertension and glaucoma [37].

Moving on to other nanotechnology-based Interventions, in 2021, J. Wang and his team developed different size dendrimer-gel particles that retain the beneficial properties of dendrimers, hydrogels, and nanoparticles. They used the polyamidoamine (PAMAM) dendrimers as building blocks of the formulation to maximize drug encapsulation. To assess the delivery effectiveness of the formulations in vivo, they used brimonidine tartrate (BT) and timolol maleate (TM) as model

drugs in vivo. As a result, studies with glaucoma mice exhibited an important decrease in IOP, both after a single dose or after a 7-day daily dosing plan [28].

A. Tuomela et al. fabricated Brinzolamide-loaded nanocrystals to examine their possible IOP-lowering effect capacity *in vivo*. Interestingly, these nanocrystal formulations remarkably decreased IOP levels [41]. Another study carried out by Liao et al. led to the development of pilocarpine-loaded gelatin-covered mesoporous silica nanoparticles. The major steps of the pilocarpineloaded gelatin-covered MSNs synthesis are described in detail in Figure 4, and *in-vivo* and *in-vitro* experiments exhibited auspicious results in IOP levels and drug delivery efficacy [42].

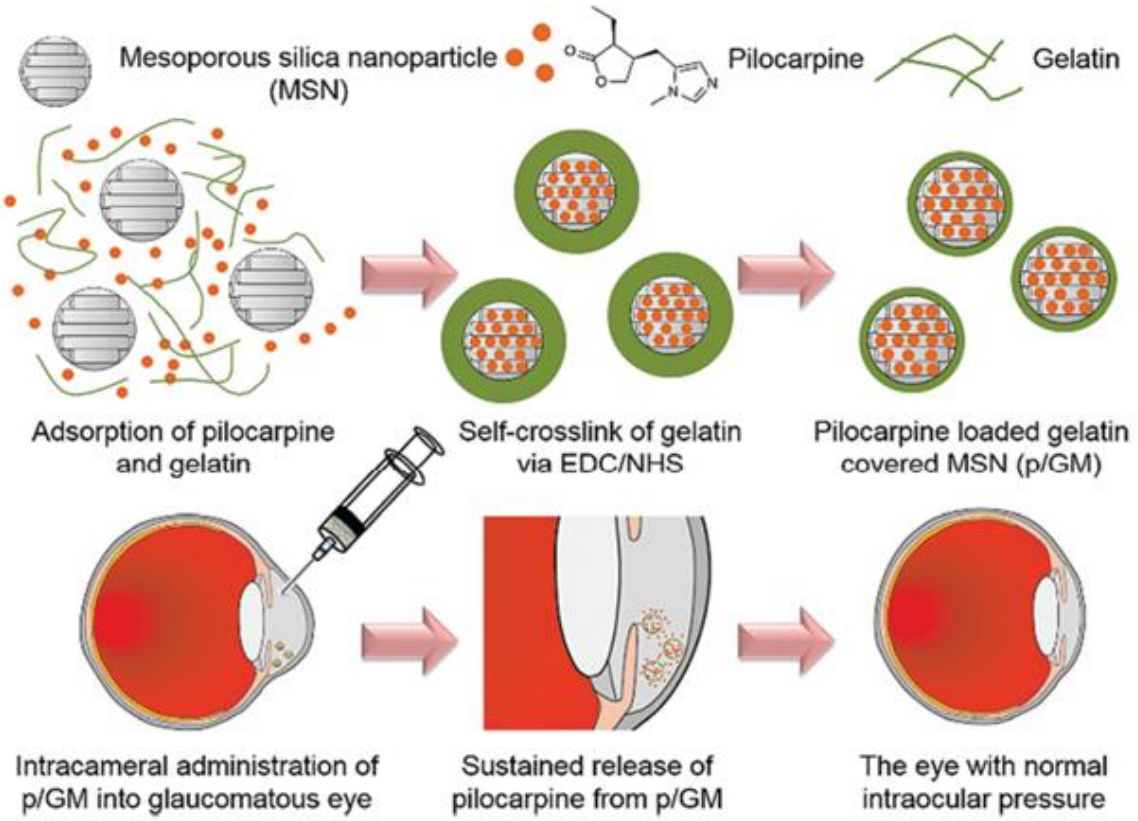

Figure 4 Schematic representation of the main steps of the pilocarpineloaded gelatin-covered MSNs synthesis [42].

Yang et al. designed a pegylated hybrid dendrimer hydrogel/poly (lactic-co-glycolic acid) nanoparticle platform that was applied topically to rabbit animal models, resulting in a steep reduction of the IOP. Likewise, Natarajan et al. developed a latanoprost-loaded liposome structure that was used to assess the therapeutic efficacy of the complex in rabbit eyes. An extremely low polydispersity index (PDI) was observed, proving the dimensional homogeneity of the nanoparticles. Latanoprost-loaded liposomes promoted a strong decrease in the IOP of the animal models after a single sub-conjunctival injection of the nano-formulation. It is important to note that the impact of drug-loaded liposomes was much larger than that of topical latanoprost medications [43]. Importantly, there are a few nanotechnology-based solutions for the treatment of glaucoma, that are at the pre-clinical stage. Table 2 summarizes the main pre-clinical stage strategies currently being examined for treating the disease.

Table 2 Main pre-clinical stage strategies for Glaucoma treatment.

Pre-clinical stage strategies for the treatment of Glaucoma	**Mode of action/Therapeutic Benefits**
Cationic-core chitosan coated micelles were formulated for the ocular delivery of diclofenac (DIC) [44].	● Stable, with minimum changed in their physical properties. ● Sustained drug release over 8 h, improving DIC bioavailability. ● Increased pre-corneal retention and penetration resulting in higher DIC concentrations in the aqueous humor. ● Minimum pre-corneal drug loss. ● Almost non-existent cytotoxicity when tested on HCEC, HLEC and L-929 cell lines after 24 h incubation (concentrations up to 5 mg/mL) [44].
Dexamethasone sodium phosphate (DSP) loaded PLGA NPs [45].	● Aid the controlled release of corticosteroid eye drops. ● Sustained DSP release over 15 days *in-vitro* under sink conditions and at least 7 days *in-vivo,* minimizing corneal graft rejection risk. ● The efficacy rates of the nano-formulation are immediate post-surgery. ● No clinical side effects were observed when tested *in-vivo,* contrary to the control group which exhibited corneal oedema and neovascularization [45].
Flurbiprofen (FLU) loaded acrylate polymer nanosuspensions [46].	● *In-vitro* experiments exhibited significant FLU controlled release from the polymeric nanosuspensions. ● Exhibited strong anti-inflammatory benefits *in-vivo,* following ocular paracentesis. ● No toxicity side-effects were observed both *in-vitro* and *in-vivo.* ● Higher FLU concentration in the aqueous humour was observed *in-vivo* [46].
Trimethyl chitosan (TMC) coated coenzyme Q10-loaded liposomes [47].	● Strong antioxidant and anti-inflammatory properties. ● Increased pre-corneal retention times of TMC-coated liposomes. ● Highlighted for the first time, the potential prophylactic effect of CoQ10, in the prevention and progression of cataract. ● CoQ10 is a strong free radical scavenger with clear anti-cataract effects *in-vivo* [47].
Axitinib-loaded nanowafer drug delivery platform [48].	● Novel and non-invasive drug delivery approach for the administration of Axitinib to the eyes. ● Slow-moving drug release, increased drug retention times, high drug absorption levels for the treatment of corneal neovascularization (CNV). ● Dissolved right after the pre-determined amount of drug is released, minimising any toxicity risks. ● Administration of axitinib-loaded nano wafer drug delivery platform once daily, exhibited better therapeutic effects compared to topical administration of axitinib, twice a day. These *in-vivo* experiments exhibited very promising results for the management of CNV [48].

Last but not least, an exciting study highlighted the neuroprotective effects of heat shock proteins (HSPs) in RGCs. Superparamagnetic nanoparticles led the introduction of HSPs via magnetic hyperthermia treatment in rat animal models, preventing the cells from programmed cell death. This approach can be used as a safe neuroprotective tool to prevent nerve cell degeneration [49].

It must be mentioned that various types of nano-formulations can be used in medical imaging. For example, quantum dots (QDs) like CdSe/ZnS core/shell nanoparticles can be used to track the lymphatic outflow of animal model eyes. QD is an ideal imaging modality because of its broad excitation spectra, limited emission spectra, and superior photobleaching capacities. Their emission spectra can change by the nanoparticle's diameter, increasing their degree of customization depending on the application [43]. Without a doubt, QDs can be used as imaging modalities for the *in-vivo* tracking of the lymphatic pathway and stimulate the development of new glaucoma therapies [50].

3.2 Optic Neuritis (ON)

Optic neuritis is frequently associated with a range of autoimmune diseases (e.g., Multiple Sclerosis, Neuromyelitis Optica spectrum disorder), viral infections and demyelinating conditions. The main features of the disease are acute visual acuity loss, visual field deficits, and colour vision abnormalities, all accompanied by pain [25, 51].

Disease diagnosis mainly involves ophthalmological examination to evaluate vision loss and optic nerve dysfunction. The main histopathological remarks of ON are damage to the optic nerve, de-myelination, and activation of inflammatory factors like macrophages, microglia, and T cells [52].

The gold standard in the treatment of ON is the administration of high corticosteroid doses to the patient to counteract the inflammatory mediators of the area [51]. Additionally, plasma exchange therapy (PE) can be used to boost vision recovery when corticosteroid treatment fails [53]. In some cases, antibiotics and antiviral medications can be used based on the disease profile of the patient (i.e., serological analysis, cell culturing, CSF analysis) [51].

3.2.1 Nanomedicine-Based Approaches for the Treatment of ON

The pathogenesis of various optic neuropathies, including Optic Neuritis, is highly affected by the production of toxic reactive oxygen species (ROS). Thus, is chief target of nanomedicine research. As Rajesh C Rao stated, regulating the activity of antioxidant enzymes *in vivo* has been shown to prevent axonal de-myelination in optic neuritis. Nanoceria, the so-called rare-earth cerium NPs with a diameter of 5 nm, were found to be strong ROS scavengers, preventing light-induced photoreceptor degeneration. These findings raise the question of whether nanoceria has a protective effect on RGCs and oligodendrocytes in conditions like optic neuritis [25].

Additionally, the transplantation of neuronal stem cells depicts a promising cell therapy approach for managing CNS disorders like ON. Recently, superparamagnetic nanoparticles have been useful for non-invasive imaging applications through magnetic tagging of the transplanted cells. Magnetic tags are taken up by the transplanted progenitor cells through endocytosis, enabling their imaging in vivo. The cells can be visualized as they grow, divide, differentiate, and re-myelinate the optic nerve [25].

3.3 Neuromyelitis Optica (NMOSD)

NMOSD is an astrocytopathy, that has been misclassified for more than a decade as an MS subtype [54]. NMOSD is designated as a different demyelinating condition right after the identification of the NMO-IgG autoantibody in 2004. This autoantibody was found to be directed against the aquaporin-4 protein (AQP4). The complement cascade is activated upon NMO-IgG and AQP4 binding, leading to astrocytic degeneration, axonal degradation, demyelination, and cell necrosis [55].

3.3.1 Current Diagnosis and Treatment

Disease diagnosis can be achieved through MRI examination of the affected areas (e.g., optic nerve, spinal cord, brainstem, cortical regions), and serological analysis will be used for the detection of NMO-IgG autoantibody (AQP4 IgG) [54, 55]. The detection of AQP4 IgG ensures the diagnosis of the disease; however, aquaporin-4 negative patients must have at least two of the following diagnostic criteria: ON, longitudinal transverse acute myelitis, area postrema syndrome, acute brainstem syndrome, narcolepsy or diencephalic syndrome, or cerebral syndrome [55].

Only symptomatic treatment is currently available through high-dose corticosteroids. However, the complete response to the treatment plan is much lower than in optic neuritis. Again, plasmapheresis is another solution that was found to facilitate vision clarity and visual fields [51].

3.3.2 Nanotechnology-Based Interventions for the Treatment of NMOSD

Focusing on a nanomedicine-based approach for the management of NMOSD, an atomic force spectroscopy (AFS) nano-sensor was introduced in 2019 to diagnose NMOSD. This nanotechnology-based sensor, with a sensitivity of 76% and a specificity of 100%, is currently the best cell-based assay for detecting AQP4-Ab. Additionally, silicon nitride rectangular cantilevers were coated with PEG, followed by immobilization of the AQP4 peptides. Here, interaction forces between NMOSD seropositive samples and AQP4 peptides were detected, not antigens. Using peptides instead of antigens brings a series of advantages, like the straightforward assembly of the sensor and the mechanism-of-action information that can be obtained through epitope mapping [55].

More recently, Akemi M. Higa and her team engineered a nanoscale biosensor for the colorimetric detection of anti-aquaporin-4 IgG by silver nanoparticles. Five different AQP4 epitopes were used to code the nanoparticles to ensure the diagnosis of seropositive patients [56].

3.4 Ischemic Optic Neuropathy (ION)

Ischemic optic neuropathy (ION) is a hypoxic condition caused by the infarction of an optic nerve fibre [57]. It is the most common form of optic neuropathy in people over 50 years old, with the ION patients reaching 90% of the cases [58].

ION is characterised by acute vision loss in the absence of pain with eye movements and severe disc oedema. It is highly consequential to distinguish ION from ON since ON is a significant risk factor for developing MS [58]. Additionally, it must be mentioned that many aspects of the disease pathogenesis remain unclear, which is why there is no effective treatment for managing the condition [58, 59]. Recent advancements in nanotechnology highlighted the field's strong potential in developing novel therapeutic strategies for the management of ION in the near future [58].

3.4.1 Dendrimers in ION Diagnosis and Treatment

Various studies evaluated the potential use of PAMAM dendrimers to selectively target activated microglia, macrophages, and other neuro-inflammatory cells. These inflammatory mediators generate reactive oxygen species (ROS), leading to the development of inflammatory ischemic lesions [60].

These nanostructures can be easily functionalized with multiple ligands, different surface groups, and surface charges to enable their internalization in the cell through endocytosis, phagocytosis, or micropinocytosis. Due to their extensive ability to be functionalized with a range of drug molecules and imaging moieties, they have received a lot of attention from the scientific community to achieve their clinical translation [61].

In their study in 2016, Y. Guo et al. examined the ability of polyamidoamine dendrimers to target the optic nerve ischemic lesions of NAION. Their experiments used rodent and non-human primate model animals with NAION lesions. Their nano-formulations were covalently conjugated to a fluorescent dye (D-Cy5) and injected systemically into the model organisms. The accumulation of the fluorescent dye in areas like the eyes and the optic nerve fibres was then assessed following the induction of both rNAION and pNAION. Upon NAION addition, the fluorescently conjugated nano-formulations were selectively accumulated in astrocytes and macrophages of the ON lesion. Interestingly, these structures can deliver nanoparticle-linked therapeutic drugs and target NAION ischemic lesions [62].

4. Safety and Toxicity Issues

Despite the beneficial effects of nanomedicine in managing various conditions, ROS production, cytotoxicity, genotoxicity, neurotoxicity, and immune activation are some of the major limiting factors that need to be considered for the development of nanocarriers [63].

Multiple mechanisms are responsible for neuronal toxicity, such as the production of ROS. For example, titanium dioxide (TiO_2) NPs boost the production of intracellular ROS in neurons and microglia. Microglia exhibit a phagocytic action when treated with silica NPs, increasing intracellular ROS and reactive nitrogen species levels. Also, hydroxylated fullerene NPs are commonly linked to cytotoxicity and phototoxicity when tested on retinal cells [63].

Other toxicity assessment studies demonstrated that various nano formulations could bypass the epithelial barrier and promote a reduction in cell viability. For example, quantum dots (QDs) significantly reduced corneal stromal cell viability in-vitro, even in low concentrations (5–20 nM). In some cases, QDs may remain in the corneal layers of animal models for up to 26 days. The long-term residence of metal-based materials in the ocular layers can promote cellular apoptosis, neurodegeneration, and corneal damage ferroptosis. A similar reduction in cellular viability has been observed with NE formulations at concentrations more than 1%. In contrast, at lower concentrations (0.1-0.5%), NE did not promote any adverse effect on cell viability [22].

Immunological activation is another type of neuronal toxicity that various nano-formulations can trigger. For instance, Au NPs can activate a series of immunological targets, including the toll-like receptor 2, granulocyte-macrophage colony-stimulating factor, and interleukin 1-alpha. Similarly, Ag NPs may trigger conformational and functional changes of neuronal spikes and inhibitory actions on the voltage-gated sodium channels on the cell membranes.

Other types of nanomaterials can promote alterations in the gene expression. For example, manganese and copper nano-systems change the expression levels of genes that regulate dopamine synthesis. In-vivo experiments with cobalt ferrite NPs exhibited a remarkable increase in the production of ROS and, subsequently, abnormally high activity of catalase, glutathione s-transferase (GST), and acid phosphatase [63]. Recent experiments on zebra fishes demonstrated that exposure to low concentrations of Ag NPs triggered developmental changes in the lens of the animal models as well as a reduction in the expression levels of some genes and proteins that modulate lens developments. Other studies proved that Ag NPs may cause DNA damage, chromosomal aberrations, and cell cycle arrest in humans, even at deficient concentrations [22]. Finally, different types of nano-systems, including dendrimers, carbon nanotubes, liposomes, and TiO_2 NPs, are associated with strong inflammatory responses and allergic reactions in animal models and humans.

It must be mentioned that NP toxicity, especially in the CNS and ocular tissues, is highly associated with many factors, such as concentration, solubility, dose, size, the shape, and the surface charge. Several studies suggest that the nano-systems' size and concentration are the principal factors that modulate the toxicological profile of the formulation. Considering the size, an interesting study exhibited that smaller silica NPs triggered microglial death dose-dependently. This was not observed with larger NPs, where no cellular death was observed. A very similar response was observed with smaller copper NPs, where cellular death was observed even in deficient concentrations. These results may be explained by the larger surface area per unit mass, which promotes stronger interactions with the surrounding milieu and higher toxicity levels. Some nano-systems exhibit strong cytotoxicity independently of their size. For example, smaller sized zinc oxide (ZnO) NPs (e.g., 10 nm, 30 nm, 200 nm) trigger neuronal cytotoxicity and cellular death, on behalf of their concentration rather than their small size.

Additionally, the charge and the functionalization on the outer surface influence the surface chemistry, toxicity, and stability of the retinal barriers. Several studies propose that positively charged nano-systems exhibit increased cellular uptake and “nano-bio” interactions, promoting crucial alteration in the normal functionality of the cell. Cationic Au NPs exhibit dramatic changes in cell viability, haemolysis, and bacterial viability compared to anionic Au NPs [63]. Another example is the hydroxyl-modified PAMAM dendrimers, which exhibited strong selectivity and reduced ocular neurotoxicity and neuroinflammation in vivo. The drug loading capacity of dendrimers is another critical parameter that must be considered. High drug loading cargoes may change the dendrimers' functionality and solubility and, subsequently, the targeting capacity of the whole system. Therefore, a balance between the drug loading levels and the possible cytotoxicity must be delicately investigated [24].

Time is another important factor that may influence neuronal cytotoxicity. Functionalized NPs may influence the biodistribution and residence time of the nanocarrier in the retinal compartment, but this may exert other problems, such as localized toxicity [63]. Additionally, in some rare cases, PLGA polymers are not fully degraded and build up in the eyes of the patients. Various factors may influence this, including the material's purity, the nanocarrier's manufacturing process, and the solvent residue [24].

It is crucial to carefully emphasize the structure, size, chemistry, charge, and surface functionalization of the nano-formulations to minimize their possible toxicity and side effects and encourage clinical translation [13].

5. Conclusions

The term nanotechnology has been derived from the Greek word nano, which means dwarf and applies in various fields of science including engineering, electronics, physics, material science, and manufacturing at a molecular level. Nanotechnology is expected to change traditional medicine significantly, developing advanced biomedical applications, including drug therapy, gene therapy, medical imaging, and drug discovery. Different nano-formulations like nanoparticles, liposomes and dendrimers led the development of nanotechnology-based drug delivery systems and disease diagnosis modalities. Due to their large surface area-to-volume ratio, these nano-formulations possess various special physicochemical properties that offer vast applications in the biomedical and pharmaceutical industry. However, despite the progress of nanotechnology in the field of medicine, scientists still need to face a lot of challenges in the management of neuro-ophthalmic conditions. First, the ocular physiological barriers and the complex anatomical structure of the eyes limit the delivery of therapeutics in the ocular cavities, minimizing their therapeutic effectiveness. Also, the pharmacokinetic profile of the ocular region is even more challenging due to the uniqueness of the ocular biochemistry, making the eyes impermeable to many active substances. Notably, traditional drug delivery methods, as well as conventional non-invasive and invasive treatment plans, may exert significant toxicity issues, greater risk, low bioavailability, and poor drug residence times. Due to these, scientists modified these nanocarriers' shape, size, and surface properties (e.g., PEGylation, surface charge) to bypass the drawbacks.

6. Future Perspectives

Without a doubt, nanotechnology may shed light on state-of-art nanodevices for ocular surgeries to manage conditions like glaucoma and retinal diseases [64]. Additionally, nanomedicine may lead to the development of novel contact lenses for the treatment of cataracts, or it can lead to the formulation of the next generation of nano-scaffolds for ocular bioengineering with neural stem cells. Focusing on ocular drug delivery, nanomedicine may facilitate the delivery of different drugs to the eyes (e.g., ocular injections, oral and transscleral drugs, and implantable nanodevices) [64]. These modern nano-formulations will exhibit better pharmacokinetic and pharmacodynamic profiles, enhanced bioavailability, better stability, increased therapeutic efficacy, greater specificity, and longer residence times with minimum side effects [65]. Interestingly, more than 1,500 ongoing clinical trials focus on drug and gene therapy for managing various ocular disorders and focusing on conserve-related ocular conditions [66].

Additionally, nanomedicine may improve biomedical imaging and screening as well as various research methodologies, such as mass spectrometry (MS), nanolithography, and nanoarrays, which could be used in the manufacturing process of novel neuro-ophthalmic drugs [64]. Advanced theranostic applications may also be developed to empower visual drug tracking during treatment plans [66]. Last but not least, nanomaterials can be used in the future for tissue regeneration purposes, cellular growth, and neuronal differentiation. Likewise, the newly developed subfields of nanorobotics and microsurgery will serve as cardinal breakthroughs in drug delivery, targeted delivery of novel interventions at both cellular and molecular levels, surgical operations, or even medical instrumentation engineering [67].

It must be mentioned that several studies showed that alongside their multiple medical benefits, various nano-formulations exhibit severe unwanted side effects. For instance, smaller nano-

formulations can bypass the physiological barriers of the eyes and reach the deeper ocular tissues. At the same time, certain shapes may enable uncontrolled cellular uptake and biodistribution from the ocular layers. Additionally, some nano-formulations have the tendency to stick to each other and form abnormal aggregates, triggering severe complications (e.g., ocular vessel occlusion and inflammation). Finally, the degradation rate of the nanocarrier, as well as their elimination rate from the organism, play a pivotal role in determining their toxicity profile.

It is widely accepted that in the future, nanomedicine-based interventions may transform the field of ophthalmology, offering innovative diagnostic and therapy solutions for managing various neuro-ophthalmological conditions. More research is required in the field to evaluate the safety of these technologies and ensure their successful clinical translation [68].

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Conceptualization, S.E., E.P.E.; writing—original draft preparation, G.S. and S.E.; methodology, G.S., S.E. and writing—review and editing, E.P.E., S.E.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Pokrajac L, Abbas A, Chrzanowski W, Dias GM, Eggleton BJ, Maguire S, et al. Nanotechnology for a sustainable future: Addressing global challenges with the international network4sustainable nanotechnology. ACS Nano. 2021; 15: 18608-18623.
2. Rambaran T, Schirhagl R. Nanotechnology from lab to industry–A look at current trends. Nanoscale Adv. 2022; 4: 3664-3675.
3. Luo D, Xie J, Zhang P, Zhu Q, Shi B, Qian L, et al. The photothermal property of zinc oxide nanoparticles in the infrared spectrum. Optik. 2020; 203: 163984.
4. Nasrollahzadeh M, Sajadi SM, Sajjadi M, Issaabadi Z. Applications of nanotechnology in daily life. Interface Sci Technol. 2019; 28: 113-143.
5. Panda PK, Sadeghi K, Seo J. Recent advances in poly (vinyl alcohol)/natural polymer based films for food packaging applications: A review. Food Packag Shelf Life. 2022; 33: 100904.
6. Juliana FR, Kesse S, Boakye-Yiadom KO, Veroniaina H, Wang H, Sun M. Promising approach in the treatment of glaucoma using nanotechnology and nanomedicine-based systems. Molecules. 2019; 24: 3805.
7. Vasconcelos T, da Silva SB, Ferreira D, Pintado M, Marques S. Cell-based in vitro models for ocular permeability studies. In: Concepts and models for drug permeability studies. Woodhead Publishing; 2016. pp. 129-154.
8. Wilson CG, Semenova EM, Hughes PM, Olejnik O. Eye structure and physiological functions. In: Enhancement in drug delivery. Boca Raton, FL: CRC Press; 2006.

9. Leclercq B, Mejlachowicz D, Behar-Cohen F. Ocular barriers and their influence on gene therapy products delivery. Pharmaceutics. 2022; 14: 998.
10. Honda M, Asai T, Oku N, Araki Y, Tanaka M, Ebihara N. Liposomes and nanotechnology in drug development: Focus on ocular targets. Int J Nanomed. 2013; 8: 495-504.
11. Sahle FF, Kim S, Niloy KK, Tahia F, Fili CV, Cooper E, et al. Nanotechnology in regenerative ophthalmology. Adv Drug Deliv Rev. 2019; 148: 290-307.
12. Nguyen CT, Acosta ML, Di Angelantonio S, Salt TE. Seeing beyond the eye: The brain connection. Front Neurosci. 2021; 15: 719717.
13. Ventura RE, Balcer LJ, Galetta SL. The neuro-ophthalmology of head trauma. Lancet Neurol. 2014; 13: 1006-1016.
14. Lee AG, Sinclair AJ, Sadaka A, Berry S, Mollan SP. Neuro-ophthalmology: Global trends in diagnosis, treatment and management. Cham, Switzerland: Springer; 2019.
15. Zarbin MA, Montemagno C, Leary JF, Ritch R. Nanotechnology in ophthalmology. Can J Ophthalmol. 2010; 45: 457-476.
16. Titov EA, Sosedova LM, Novikov MA, Zvereva MV, Rukavishnikov VS, Lakhman OL. The analysis of acute and subacute toxicity of silver selenide nanoparticles encapsulated in arabinogalactan polymer matrix. Polymers. 2022; 14: 3200.
17. Dash P, Panda PK, Su C, Lin YC, Sakthivel R, Chen SL, et al. Near-infrared-driven upconversion nanoparticles with photocatalysts through water-splitting towards cancer treatment. J Mater Chem B. 2024; 12: 3881-3907.
18. Shaheen N, Khaled M, Seo S, Bezchlibnyk Y, Flouty O, Bharmauria V. Neurostimulation in neuro-ophthalmology: Mechanisms and therapeutic potential. In: Current concepts in neuro-ophthalmology. Rijeka, Croatia: IntechOpen; 2024.
19. Naher HS, Al-Turaihi BA, Mohammed SH, Naser SM, Albark MA, Madlool HA, et al. Upconversion nanoparticles (UCNPs): Synthesis methods, imaging and cancer therapy. J Drug Deliv Sci Technol. 2023; 80: 104175.
20. Tang Z, Fan X, Chen Y, Gu P. Ocular nanomedicine. Adv Sci. 2022; 9: 2003699.
21. Scheive M, Yazdani S, Hajrasouliha AR. The utility and risks of therapeutic nanotechnology in the retina. Ther Adv Ophthalmol. 2021; 13: 25158414211003381.
22. Yang C, Yang J, Lu A, Gong J, Yang Y, Lin X, et al. Nanoparticles in ocular applications and their potential toxicity. Front Mol Biosci. 2022; 9: 931759.
23. Gómez-Garzón M, Martínez-Ceballos MA, Gómez-López A, Rojas-Villarraga A. Application of nanotechnology in ophthalmology: Where are we? Charact Appl Nanomater. 2022; 5: 66-78.
24. Meng T, Kulkarni V, Simmers R, Brar V, Xu Q. Therapeutic implications of nanomedicine for ocular drug delivery. Drug Discov Today. 2019; 24: 1524-1538.
25. Chen DF, Rao RC. Nanomedicine and optic nerve regeneration—Implications for ophthalmology. US Ophthalmic Rev. 2011; 4: 108-111.
26. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. Neurol. 2004; 62: 177-180.
27. Fea AM, Novarese C, Caselgrandi P, Boscia G. Glaucoma treatment and hydrogel: Current insights and state of the art. Gels. 2022; 8: 510.
28. Wang J, Li B, Huang D, Norat P, Grannonico M, Cooper RC, et al. Nano-in-nano dendrimer gel particles for efficient topical delivery of antiglaucoma drugs into the eye. Chem Eng J. 2021; 425: 130498.

29. Hagan S, Martin E, Enríquez-de-Salamanca A. Tear fluid biomarkers in ocular and systemic disease: Potential use for predictive, preventive and personalised medicine. EPMA J. 2016; 7: 15.
30. Glaucoma Research Foundation. Types of Eye Drops for Glaucoma [Internet]. San Francisco, CA: Glaucoma Research Foundation. Available from: https://glaucoma.org/treatment/medication/eyedrops.
31. Dikopf MS, Vajaranant TS, Edward DP. Topical treatment of glaucoma: Established and emerging pharmacology. Expert Opin Pharmacother. 2017; 18: 885-898.
32. Heel RC, Brogden RN, Speight TM, Avery GS. Timolol: A review of its therapeutic efficacy in the topical treatment of glaucoma. Drugs. 1979; 17: 38-55.
33. Munroe WP, Rindone JP, Kershner RM, D'Arcy PF. Systemic side effects associated with the ophthalmic administration of timolol. Drug Intell Clin Pharm. 1985; 19: 85-89.
34. Faiq MA, Wollstein G, Schuman JS, Chan KC. Cholinergic nervous system and glaucoma: From basic science to clinical applications. Prog Retin Eye Res. 2019; 72: 100767.
35. Schlote T. Side-effects and risk profile of latanoprost 0.005% (Xalatan). Ophthalmologe. 2002; 99: 724-729.
36. Moshirfar M, Parker L, Birdsong OC, Ronquillo YC, Hofstedt D, Shah TJ, et al. Use of Rho kinase inhibitors in ophthalmology: A review of the literature. Med Hypothesis Discov Innov Ophthalmol. 2018; 7: 101.
37. Chae JJ, Jung JH, Zhu W, Gerberich BG, Bahrani Fard MR, Grossniklaus HE, et al. Drug-free, nonsurgical reduction of intraocular pressure for four months after suprachoroidal injection of hyaluronic acid hydrogel. Adv Sci. 2021; 8: 2001908.
38. Maulvi FA, Soni PD, Patel PJ, Desai AR, Desai DT, Shukla MR, et al. Controlled bimatoprost release from graphene oxide laden contact lenses: In vitro and in vivo studies. Colloids Surf B Biointerfaces. 2021; 208: 112096.
39. Sekar P, Chauhan A. Effect of vitamin-E integration on delivery of prostaglandin analogs from therapeutic lenses. J Colloid Interface Sci. 2019; 539: 457-467.
40. Cheng YH, Ko YC, Chang YF, Huang SH, Liu CJ. Thermosensitive chitosan-gelatin-based hydrogel containing curcumin-loaded nanoparticles and latanoprost as a dual-drug delivery system for glaucoma treatment. Exp Eye Res. 2019; 179: 179-187.
41. Tuomela A, Liu P, Puranen J, Rönkkö S, Laaksonen T, Kalesnykas G, et al. Brinzolamide nanocrystal formulations for ophthalmic delivery: Reduction of elevated intraocular pressure in vivo. Int J Pharm. 2014; 467: 34-41.
42. Liao YT, Lee CH, Chen ST, Lai JY, Wu KC. Gelatin-functionalized mesoporous silica nanoparticles with sustained release properties for intracameral pharmacotherapy of glaucoma. J Mater Chem B. 2017; 5: 7008-7013.
43. Kim NJ, Harris A, Gerber A, Tobe LA, Amireskandari A, Huck A, et al. Nanotechnology and glaucoma: A review of the potential implications of glaucoma nanomedicine. Br J Ophthalmol. 2014; 98: 427-431.
44. Shi S, Zhang Z, Luo Z, Yu J, Liang R, Li X, et al. Chitosan grafted methoxy poly (ethylene glycol)-poly (ε-caprolactone) nanosuspension for ocular delivery of hydrophobic diclofenac. Sci Rep. 2015; 5: 11337.

45. Pan Q, Xu Q, Boylan NJ, Lamb NW, Emmert DG, Yang JC, et al. Corticosteroid-loaded biodegradable nanoparticles for prevention of corneal allograft rejection in rats. J Control Release. 2015; 201: 32-40.
46. Pignatello R, Bucolo C, Spedalieri G, Maltese A, Puglisi G. Flurbiprofen-loaded acrylate polymer nanosuspensions for ophthalmic application. Biomaterials. 2002; 23: 3247-3255.
47. Zhang J, Wang S. Topical use of coenzyme Q10-loaded liposomes coated with trimethyl chitosan: Tolerance, precorneal retention and anti-cataract effect. Int J Pharm. 2009; 372: 66-75.
48. Yuan X, Marcano DC, Shin CS, Hua X, Isenhart LC, Pflugfelder SC, et al. Ocular drug delivery nanowafer with enhanced therapeutic efficacy. ACS Nano. 2015; 9: 1749-1758.
49. Alqawlaq S, Huzil JT, Ivanova MV, Foldvari M. Challenges in neuroprotective nanomedicine development: Progress towards noninvasive gene therapy of glaucoma. Nanomedicine. 2012; 7: 1067-1083.
50. Tam AL, Gupta N, Zhang Z, Yücel YH. Quantum dots trace lymphatic drainage from the mouse eye. Nanotechnology. 2011; 22: 425101.
51. Bennett JL. Optic neuritis. Contin Lifelong Learn Neurol. 2019; 25: 1236-1264.
52. Aneesh A, Liu A, Moss HE, Feinstein D, Ravindran S, Mathew B, et al. Emerging concepts in the treatment of optic neuritis: Mesenchymal stem cell-derived extracellular vesicles. Stem Cell Res Ther. 2021; 12: 594.
53. Fu J, Wang Y, Li H, Zhou H, Song H, Sun M, et al. Efficacy of plasma exchange treatment for demyelinating optic neuritis associated with various serum antibodies: A prospective cohort study. Neurol Ther. 2022; 11: 797-813.
54. Phuljhele S, Kedar S, Saxena R. Approach to optic neuritis: An update. Indian J Ophthalmol. 2021; 69: 2266-2276.
55. de Souza Moraes A, Brum DG, Ierich JC, Higa AM, Assis AS, Miyazaki CM, et al. A highly specific and sensitive nanoimmunosensor for the diagnosis of neuromyelitis optica spectrum disorders. Sci Rep. 2019; 9: 16136.
56. Higa AM, Moraes AS, Shimizu FM, Bueno RG, Peroni LA, Strixino FT, et al. Anti-aquaporin-4 immunoglobulin G colorimetric detection by silver nanoparticles. Nanomedicine. 2022; 41: 102531.
57. Patel HR, Margo CE. Pathology of ischemic optic neuropathy. Arch Pathol Lab Med. 2017; 141: 162-166.
58. Biousse V, Newman NJ. Ischemic optic neuropathies. N Engl J Med. 2015; 372: 2428-2436.
59. DelMonte DW, Bhatti MT. Ischemic optic neuropathy. Int Ophthalmol Clin. 2009; 49: 35-62.
60. Mishra MK, Beaty CA, Lesniak WG, Kambhampati SP, Zhang F, Wilson MA, et al. Dendrimer brain uptake and targeted therapy for brain injury in a large animal model of hypothermic circulatory arrest. ACS Nano. 2014; 8: 2134-2147.
61. Kambhampati SP, Kannan RM. Dendrimer nanoparticles for ocular drug delivery. J Ocul Pharmacol Ther. 2013; 29: 151-165.
62. Guo Y, Johnson MA, Mehrabian Z, Mishra MK, Kannan R, Miller NR, et al. Dendrimers target the ischemic lesion in rodent and primate models of nonarteritic anterior ischemic optic neuropathy. PloS One. 2016; 11: e0154437.
63. Kamaleddin MA. Nano-ophthalmology: Applications and considerations. Nanomedicine. 2017; 13: 1459-1472.

64. Sahoo SK, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug Discov Today. 2008; 13: 144-151.
65. Shah N. Nanocarriers: Drug delivery system. Singapore: Springer; 2021.
66. Weng Y, Liu J, Jin S, Guo W, Liang X, Hu Z. Nanotechnology-based strategies for treatment of ocular disease. Acta Pharm Sin B. 2017; 7: 281-291.
67. Rajendran S, Sundararajan P, Awasthi A, Rajendran S. Nanorobotics in Medicine: A Systematic Review of advances, challenges, and future prospects. arXiv. 2023. doi: 10.48550/arXiv.2309.10881.
68. Wei J, Mu J, Tang Y, Qin D, Duan J, Wu A. Next-generation nanomaterials: Advancing ocular anti-inflammatory drug therapy. J Nanobiotechnol. 2023; 21: 282.