WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 8.025
Volume 13, Issue 11, 1193-1208 Review Article ISSN 2278 – 4357

GLAUCOMA MANAGEMENT VIA NANOTECHNOLOGY: A REVIEW

Ritik G. Ahire[1], Prafulla A. Ahire[2]*, Nikita R. Sonawane[3], Imtiaz T. Ansari[4] and Ravindra R. Patil[5]

[1,2,3]Jijamata Education Society's College of Pharmacy, Nandurbar (425412), Maharashtra (India).

[4]Department of Pharmacology, Jijamata Education Society's College of Pharmacy, Nandurbar (425412), Dist-Nandurbar, Maharashtra (India).

[5]Department of Pharmaceutical Chemistry, Jijamata Education Society's College of Pharmacy, Nandurbar (425412), Dist-Nandurbar, Maharashtra (India).

Article Received on
19 September 2024,

Revised on 09 October 2024,
Accepted on 29 October 2024

DOI: 10.20959/wjpps202411-28560

***Corresponding Author**
Prafulla A. Ahire
Jijamata Education Society's College of Pharmacy, Nandurbar (425412), Maharashtra (India).

ABSTRACT

Retinal ganglion cell (RGC) breakdown is a hallmark of glaucoma, a condition that predominantly affects the optic nerve and is one of the primary causes of irreversible blindness. While elevated intraocular pressure (IOP) is a significant risk factor, other contributors include genetics, systemic conditions, and environmental factors. Traditional treatments often fall short, facing challenges such as inadequate IOP control and systemic side effects. Recent advancements in nanotechnology offer promising alternatives, enhancing drug delivery through engineered nanoparticles, liposomes, and dendrimers. These novel systems improve drug bioavailability, ensure targeted delivery to ocular tissues, and enable sustained release, thereby minimizing toxicity and enhancing therapeutic efficacy. The pathophysiology of various glaucoma types, including primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG), is complex and multifactorial, necessitating tailored treatment strategies. Genetic factors also play a crucial role, with specific genes implicated in different glaucoma forms. Comprehensive evaluations combining medical history, visual field testing, IOP measurement, and advanced imaging techniques like Optical Coherence Tomography (OCT) are vital for accurate diagnosis. Nanomedicine, characterized by its nanoscale innovations, addresses the challenges of conventional drug delivery systems. It provides a platform for combinatorial therapies that target multiple pathophysiological

processes simultaneously, thus enhancing treatment outcomes. Future research should focus on novel nanomaterials, implantable devices for sustained drug release, and gene therapy approaches. By leveraging these advancements, the management of glaucoma can be revolutionized, ultimately improving patient adherence, comfort, and quality of life.

KEYWORDS: Glaucoma, Nanotechnology, POAG, NTG, Novel Drug Delivery.

INTRODUCTION

Glaucoma is a family of ocular diseases that affect the optic nerve. Although intraocular pressure (IOP) is frequently linked to glaucoma, other factors that may contribute to the condition include high blood pressure, migraines, obesity, ethnicity, and family history. The optic nerve is harmed by high IOP. The elderly and those over 60 are most affected by this condition. The Optic Nerve Head (ONH), a section of the Optic Disc (OD), is where the optic nerve degeneration occurs. The injury caused by glaucoma is largely irreparable, and all types of the condition are irreversible. The patients' only options are strategies to reduce the disease's rate of progress. Early detection of disease is essential to the effectiveness of all therapy.[1] Among the drawbacks of conventional treatments are frequently insufficient intraocular pressure control, systemic adverse effects, and poor medication delivery. Nanotechnology is a game-changer because it provides focused, effective, and minimally invasive solutions. Nanoparticles, liposomes, and dendrimers are engineered to: Enhance drug bioavailability and solubility, Target specific ocular tissues, provide sustained release and controlled delivery, and reduce systemic toxicity. They have also improved efficacy, reduced side effects, personalized medicine, Non-invasive or minimally invasive.

Pathophysiology

Eye diseases Glaucoma represents a grave ocular disease. Several factors, including age, diabetes, hypertension, and myopia, can lead to this irreversible visual loss. There are other variations of the illness, such as POAG, PACs, and NTG. Its pathogenesis must be understood for a proper diagnosis and course of treatment.

Eye diseases Retinal ganglion cells (RGCs) and their axons sustain early disease damage, which leads to vision loss, even though the pathophysiology of POAG is unknown. Risk factors include a thin middle cornea, advanced age, and high intraocular pressure (IOP). Even though lowering IOP with surgery or medication is the aim of POAG therapy, many patients nevertheless gradually lose their field of vision. Neuroprotective strategies and RGC axon

regeneration therapies are examples of additional medications under investigation.[2] Pupillary block, anterior lens movement, and lens convexity are a few of the variables that might cause angle closure (PAC). An increase in intraocular pressure occurs when the angle closes from superior to inferior. Pupillary block is the most common cause. It causes iris bending, angle appositional closure, and a larger pressure differential between the anterior and posterior chambers of the eye. Shallow anterior chambers are more prone to pupilar block, and iris thickness can affect the pressure differential between both chambers. Greater iris convexity is caused by anteriorly positioned lenses, which are important in the pathophysiology of PAC. Lens movement forward, as observed in progressive cataract phacomorphic glaucoma[3] intraocular pressure (IOP), which might raise susceptibility to glaucomatous damage, is one of the many complicated elements that define non-trial glaucoma (NTG). The axons, capillaries, and astrocytes can sustain harm due to deformation associated with IOP. Low IOP can cause CSF compartment syndrome and progressive optic neuropathy, which both lower the body's ability to remove hazardous substances. The pathophysiology of NTG can also be attributed to inadequate blood flow, vascular dysregulation, systemic hypotension, and sleep apnea/hypopnea syndrome. Another cause is basic vascular dysfunction, which is more common in Asians and women.[4]

Genetics

The genetics of glaucoma are complex and multifactorial, involving various genes and inheritance patterns. Here's an overview:

Types of glaucoma with genetic components

Primary Open-Angle Glaucoma (POAG): Associated with multiple genetic variants.

Primary open-angle glaucoma is the most common kind of disease in most individuals worldwide.[5] POAG individuals have high intraocular pressure as a risk factor for glaucoma development, even when their ocular structures are normal. Up to one-third of the individuals in the NTG POAG subgroup have normal IOP.[6] Compared to POAG, those with NTG may be more vulnerable to optic nerve degeneration.[7]

Normal-Tension Glaucoma (NTG): Associated with OPA1, OPTN, and TBK1 genes.

The pathophysiology of NTG is diverse, involving several genes. A potential hereditary susceptibility to NTG is suggested by the existence of a family history in NTG cases.[11] NTG is thought to be caused by variations in genes such as myocilin (MYOC), optineurin (OPTN), and WD repeat-containing protein 36 (WDR36), though more research is needed to confirm

this.[8,9] Hereditary NTG may be connected to the ocular atrophy type 1 (OPA1) gene, which is involved in mitochondrial function and causes RGC apoptosis. TANK binding kinase gene mutations have been linked to severe VF defects in NTG. 1 (TBK1), endothelin receptor type A (EDNRA), and toll-like receptor 4 (TLR4).[10]

Primary Angle-Closure Glaucoma (ACG): Linked to genetic variants in PLEKHA7 and COL11A1.

PACG is a major cause of permanent lack of vision, especially in Asia. In patients with PACG, signs may be acute, subacute, or chronic. Greater intraocular pressure is caused in PACG patients independent of symptoms because of the opposition of the peripheral iris and trabecular meshwork, which creates a barrier to fluid flowing out of the eye. An extremely high IOP caused by PACG may cause the optic nerve to deteriorate.[11] Research indicates that PACG may have a genetic component even if no environmental risk factors exist. Human family aggregation of early-onset angle-closure glaucoma is included in the spectrum of nanophthalmos, a severe form of hyperopia that can result in angle closure as a result of age-related lens enlargement. Nanopthalmos, a hereditary autosomal dominant or recessive disorder, is caused by mutations in the MFRP and TMEM98 genes. Aberrant BEST1 can lead to Bestrophinopathy, an autosomal recessive form of retinal degeneration that often coexists with angle closure glaucoma.[12]

Genetic risk factors

1. MYOC (Myocilin): Mutations increase POAG risk.
2. OPTN (Optineurin): Mutations associated with NTG.
3. TBK1 (TANK-binding kinase 1): Mutations linked to NTG.
4. CYP1B1 (Cytochrome P450 1B1): Mutations cause PCG.
5. FOXC1 (Forkhead box C1): Mutations associated with PCG.[13]

Inheritance patterns

1. Autosomal Dominant: POAG, PCG.
2. Autosomal Recessive: PCG.
3. X-linked: Some cases of PCG.[14]

Evaluation & Diagnosis

Clinical evaluation

Medical history: Assessing symptoms, family history, and previous eye conditions.

Visual acuity: Measuring central vision using Snellen charts.

Visual field testing

The use of static automated visual field testing is now part of the diagnosis and Roni coring process for primary open-angle glaucoma. The interpretation of the vast volumes of data generated by this equipment is not automated, even though many testing-related tasks are. Identifying the differences between a patient's normal vision areas and those of a patient with early glaucoma, as well as determining whether slight decreases in sensitivity are the result of a real defect or a byproduct of other variables, are two of the practitioner's biggest concerns. In addition to some of the other testing methods available for the evaluation of glaucoma, This study offers a clinical review of the systematic analysis of the field of vision graphs to find errors caused by patient factors.[15]

Intraocular pressure (IOP) measurement

In particular, individuals with glaucoma, ocular hypertension, and those with risk factors for the condition require intraocular pressure (IOP) measurements during optical examinations. Although Goldmann applanation tonometry (GAT) is still the gold standard for measuring intraocular pressure (IOP), it is dependent on several corneal variables, requires local anesthetics, and can be difficult to administer to youngsters, patients with limited compliance, and patients undergoing surgery. Numerous tonometers have been proposed in the past to address the problems with GAT. The authors examine the many intraocular pressure (IOP) measurement instruments now in use, stressing their primary benefits and drawbacks. An essential first step will be the ongoing monitoring of IOP, which is now being assessed.[16]

Pupil examination

Progressive loss of retinal ganglion cells and their optic nerve axons causes anatomical and functional impairments (loss of vision field and damage to the optic disc) in glaucoma. Retinal nerve fiber loss frequently occurs asymmetrically in the upper and lower retina, and damage from glaucoma is sometimes more severe in one eye. To detect glaucoma patients, diagnostic methods can make use of this asymmetry. The afferent input from the retina and optic nerve is indicated by the pupillary light reflex (PLR). Referred to as a "relative afferent pupillary defect" (RAPD), asymmetry in the PLR between the two eyes is frequently an indication of unilateral or asymmetric impairment of the anterior afferent visual pathways.

RAPDs are frequently clinically observable in glaucoma patients. Several methods for measuring or quantifying a RAPD have been described. They include the swinging flashlight test (SFT), which measures the pupillary response more accurately by subjectively rating each pupil's initial constriction and subsequent redilation in response to a bright light swinging, either with or without the use of neutral density filters.

Further improvements in the measurement of the pupillary response to light have been made possible by the development of pupillography. Six Some have employed pupil perimetry to track pupillary constriction in response to perimetric light stimuli aimed at various regions of the retina to assess the visual field objectively. We examined methods for assessing and quantifying PLR in glaucoma patients in this study. Additionally, we evaluated how accurate those methods were in identifying glaucoma.[17]

Corneal thickness measurement

One sensitive measure of corneal health is corneal thickness and function which is simple to measure. It displays both structural alterations and endothelial pump function inside the stroma. A lower central corneal thickness (CCT) is a crucial metric to assess in the treatment of glaucoma. The possibility of developing ocular hypertension (OHT) into POAG (primary open-angle glaucoma)1 in addition to already glaucoma treatment. The best standard used today to measure corneal Ultrasound pachymetry (USP) measures thickness. Research has demonstrated minimal variability between and between observers. The need for topical anesthesia, the probe's contact with the cornea, and the doctor's experience are among the four to six disadvantages. CCT instability7 may result after topical anesthetics and the process may result in patient epithelial erosion, and discomfort.[18]

Diagnostic tests

Optical Coherence Tomography (OCT)

The diagnosis of glaucoma depends on both the anatomical examination of the retina and optic nerve as well as the functional evaluation of the patient's eyesight. OCT was a breakthrough in the treatment of glaucoma because it could observe the retinal substructure. Automated segmentation of the retinal layers allowed for the objective assessment of the retinal tissue layers, including the ONH, peripapillary region, and macula. By evaluating whether structures are borderline or outside of normal limits, clinicians can better recognize and track the evolution of sickness by comparing these measures with established normative

databases. Before changes in the visual field, RNFL thinning is often one of the first signs of glaucoma.[19]

Ultrasound bio-microscopy (UBM)

Ultrasound biomicroscopy (UBM) is a vital diagnostic, evaluation, and follow-up technique for glaucoma patients. The mechanism of angle closure can be found even in individuals with primary open-angle glaucoma (POAG) or primary angle closure glaucoma (PACG) by doing a UBM. UBM can assess eye structures at the microscopic level. The cornea, which appears as a curving hyperreflective line, is the most anterior structure. Its components, thickness, and shape can all be assessed. Because of its superficial location, a high-resolution transducer can be used to measure not only the global thickness but also the thickness of its constituent parts, including the epithelium. The anterior chamber (AC) is found in front of the iris and behind the cornea. UBM imaging may be used to measure its dimensions and provide information about its shape, composition, and angle. AC depth should typically be between 2.5 and 3.0 mm, although there are large variances.[20]

Scanning laser polarimetry

The scanning laser polarimeter (Nerve Fiber Analyzer [NFA]–GDx or NFA II; Laser Diagnostic Technologies, San Diego, Calif.) doubles as a confocal scanner laser ophthalmoscope thanks to its inbuilt polarization modifier. Its operational details have been previously disclosed. Through the utilization of the eye's optical medium, a single spot of the retina is illuminated by the light source, a 780 nm polarization-modulated laser beam. Finding the reflected light that double-passes the RNFL at that spot allows one to calculate the retardation there. The retardation map is produced by progressively focusing the laser beam over each of the 256×256 retinal sites, assigning a corresponding retardation value to each retinal location (pixel). We used a field of view that was around 15°. The collection time for these 65,536 data sets was 0.7 seconds. The only distinction between the NFA-GDx and the NFA II is the presence of a normative database and a screening mode, neither of which we utilized.[21]

Treatment

Nanomedicine

Nanotechnology is the study of science, engineering, and technology at the 1–10 nm nanoscale. The founder of nanotechnology, Richard Feynman, suggested modifying molecules and atoms using microscopic machinery.[22] The term "nanomedicine" describes

technology that helps cure and diagnose diseases at the molecular level, or that monitors, controls, builds, repairs, defends, and enhances human biological systems.[23]

The size of the nanoparticles, which can be predicted using quantum mechanics, is what defines nanotechnology. Compared to macro-scale materials, nanomaterials provide a greater variety of synthetic reactions due to their distinct chemical and physical properties. The medical community is now interested in them because to their electric conductivity, biocompatibility, magnetic properties, and biodegradable properties The medical profession is now interested in them because of their electric conductivity, biocompatibility, magnetic properties, and biodegradability.[24]

Nanomedicine as novel drug delivery system

The eye illness glaucoma is defined by the progressive erosion and functional aggravation of the optic nerve, which results in a loss of visual sensitivity and eventual blindness.[25] The elderly may find it difficult to stick to treatment regimens including topical medicine or eye drops, as they may have decreased physical dexterity. It is essential to develop a novel drug delivery system that can release the medication gradually over several months with just one dose.[22] Drug delivery is commonly achieved by the use of nanoparticles, nanodiamonds, nanocrystals, dendrimers, nanosuspension, niosomes, liposomes, and other devices. These nanoparticles can integrate pharmaceuticals by conjugation or encapsulation on their surface, improving and offsetting the drawbacks of traditional therapy. Hydrogels can also be modified with inorganic nanoparticles to replicate the sustained release mechanical feature of contact lenses.[26]

The medication kind, target tissue, and administration route are some of the parameters that impact the choice of drug delivery method. Targeted distribution, bioavailability, prolonged release, dosage accuracy, longer shelf life, less tissue irritation, and improved solubility are all provided by drug delivery systems based on nanotechnology.[27,28] Despite its widespread use, topical administration of glaucoma medications is still hampered by limited bioavailability and poor corneal permeability. Through surface functionalization, nanoparticles can increase their precorneal retention period and hence enhance effectiveness. Although endocytic pathways allow them to enter cells, one must take into account the toxicity of nanomaterials. Numerous biological models have been employed to assess possible toxicity; nonetheless, the majority demonstrate oxidative stress and impaired visual

systems during exposure to inorganic nanoparticles. Therefore, the harmful effects of the nanoparticles determine the efficacy and safety of glaucoma treatment.[29]

Liposomes

Liposomes are biocompatible synthesized phospholipid bilayers that can be used to deliver hydrophilic and hydrophobic drugs to the body. They can transport drug molecules to their intended targets while encasing and shielding solutes. Drug molecules can be engineered into liposomes with increased bioavailability, bioefficacy, and prolonged release. Because of their sensitivity to changeable triggers including pH levels, electromagnetic waves, and thermosensitivity, the release of trapped molecules may be strictly controlled.[30] The surface charge of the liposomes has a major impact on the duration of drug interaction at the corneal epithelium's surface. Positively charged liposomes have better corneal penetration and encapsulation efficiency than neutral or negative-charged liposomes.[31]

Clinical applications of conventional liposomes are limited by their propensity to agglomerate, leaking of encapsulated medication, and phagocytosis susceptibility. Changing the liposomes' surface properties has assisted in overcoming these limitations. Liposomes have been coated with bioadhesive polymers, which have the effect of preventing aggregation and raising their viscosity. In an in vitro drug release investigation, timolotil maleate chitosan-coated liposomes (TMCHL) increased the corneal permeability coefficient by 3.18 times.[32]

The effectiveness and safety of drug-loaded Nano liposomes in the treatment of glaucoma have been investigated in recent clinical trials. In rabbits, dorzolamide (DRZ)-loaded nanoliposomes outperformed commercially available formulations in terms of IOP reduction.[33] In 6 participants with ocular hypertension or primary open-angle glaucoma, lipomal latanoprost injections were given once in the subconjunctival tissue.[34]

Niosomes

The hydrophilic and hydrophobic medications are carried via niosomes, which are circular, closed bilayer structures of non-ionic amphiphiles that are inexpensive. With chitosan-coated niosomes decreasing rabbits' IOP and multilamellar niosomes entrapping greater dosages, they offer therapeutic efficacy and longer bioavailability.[35]

Polymeric nanoparticles

Polymeric nanoparticles are spherical particles that can pass right through biological membranes and get drugs to the right organs. First-generation, second-generation, and third-generation are the three groups into which they fall. Pilocarpine-loaded nanoparticles lower IOP without causing side effects, PGT-loaded nanoparticles release timolol for a longer period, and Eudragit nanoparticles containing ACZ enhance ocular tissue permeability.[36]

Dendrimers

Dendrimers, flexible polymers with large surface areas, can accommodate drugs due to their nonimmunogenic and biocompatible properties. They offer longer residual time, less discomfort, and higher absorption compared to commercial eye drop formulations.[37]

Nanosuspension

Nanosuspensions, composed of solid particles in the liquid phase, can increase lipophilic medications' bioavailability and be easily incorporated into hydrogels. Ion Exchange Resins (IERs) provide competitive binding and shielding for ionic medications.[24] Butanol-loaded nanoparticles have been authorized for ocular medication delivery, with no discernible difference in intraocular pressure lowering but a reduced prevalence of ocular pain.[38]

Cyclodextrin complex

Three kinds of cyclic oligosaccharides with sugar molecules resembling rings are called cyclodextrins: α–, β–, and γ–cyclodextrins. Lipophilic medicines can pass through the corneal surface because they facilitate drug transport without changing their structural makeup. Examples include the BZL-hydro propyl-ß-cyclodextrin inclusion complex in nanoliposomes and the sulfobutyl ether of the beta-cyclodextrin complex for pilocarpine.[39]

Nanocrystals

Small crystalline particles, known as nanocrystals, possess a high surface area and strong bioavailability without the need for carriers. Their diameter is less than 1 μm. While cellulose nanocrystals and triblock poloxamer co-polymer formulations had higher sustained drug release, BZL nanocrystals showed higher efficacy in decreasing IOP.[40]

Future prospective

Combinatorially tailored nanomedicine

A combination of treatment medicines that target various pathophysiological processes in glaucomatous conditions may be more beneficial than monotherapy, given that glaucoma is a multifactorial neurodegenerative disease of RGCs.[41] Conventional topical antiglaucoma eye drops make it difficult to deliver more than one therapeutic agent with different physicochemical characteristics at the same time. However, nanocarrier systems allow for the simultaneous delivery of numerous therapeutic moieties. For instance, Chan and associates developed a thermo-sensitive PLGAPEG-PLGA co-polymer that simultaneously conveyance hydrophilic and hydrophobic compounds (rhodamine B and coumarin 6). For up to four weeks, a single subconjunctival injection of the produced nano platform may produce a high drug concentration. In the future, tailored combinatorial therapy based on nano drug carriers and tailored to each patient's physiological profile may be a common option for treating glaucoma.[42]

System for delivering combination nano drugs

Through the entrapment or embedding of nanoparticles (NPs) into electrospun nanofibers (NFs), a hybrid nano system is developed. Comparing a hybrid nanodrug delivery system to a single-originated nano system, the former minimizes the disadvantages of each component while preserving the benefits of the latter. Additionally, entrapped NPs enhance the total surface area for pharmacological drug attachment. When relatively poor biocompatibility NPs are mixed with high biocompatibility polymers, for instance, the external polymer matrixes may protect the drug load and embed the NPs in living tissues, enhancing drug release activities and reducing bio-toxicity. Improved retinal residence, extended interaction time, accurate dose delivery, sustained drug release, decreased dosing frequency, enhanced bioavailability, and less potential for adverse effects are some benefits of using NPs in electrospun NFs.[43]

CONCLUSION

Innovative treatments are required for glaucoma, a major cause of permanent blindness. Novel drug delivery techniques that are based on nanotechnology present encouraging alternatives. This review focuses on how nanotechnology has enabled the treatment of glaucoma. Treatment for glaucoma has been transformed by nanotechnology, which has produced amazing breakthroughs. Important discoveries include improved drug

administration using dendrimers, liposomes, and nanoparticles, increasing bioavailability and facilitating targeted ocular distribution. Therapeutic efficacy is increased by controlled distribution and sustained release methods. The targeted distribution also ensures patient safety by reducing systemic toxicity. These innovations change the way glaucoma is managed, enhance patient compliance, and maximize treatment results. Treatment Implications of Nanotechnology for Glaucoma: The treatment of glaucoma with nanotechnology has significant effects on patient care. Increasing adherence, streamlining treatment plans, and lowering dosage frequency all contribute to better patient compliance. Improved therapeutic results are another benefit of targeted delivery, which maximizes medication effectiveness and illness control. Furthermore, enhanced patient comfort and safety are guaranteed by the reduced chance of systemic side effects. In the end, nanotechnology gives glaucoma sufferers more individualized and efficient therapy options. This complex effect changes the way glaucoma is managed, improving patient outcomes and quality of life. Future studies should focus on three main areas to improve glaucoma therapy. First, new medication transport, bioavailability, and therapeutic efficacy will be unlocked by researching innovative nanomaterials and formulations. Secondly, developing implantable nanodevices for sustained release will revolutionize treatment regimens, ensuring consistent and optimal drug concentrations. Lastly, exploring gene therapy and stem cell-based approaches will unveil innovative, non-traditional treatments, potentially reversing or halting glaucoma progression. By pursuing these avenues, researchers can overcome existing limitations, improve patient outcomes, and ultimately transform the glaucoma treatment landscape.

REFERENCES

1. Shalaby WS, Ahmed OM, Waisbourd M, Katz LJ. A review of potential novel glaucoma therapeutic options independent of intraocular pressure. Survey of Ophthalmology, 2022; 1, 67(4): 1062-80.
2. Weinreb RN, Leung CK, Crowston JG, Medeiros FA, Friedman DS, Wiggs JL, Martin KR. Primary open-angle glaucoma. Nature reviews Disease primers, 2016; 22, 2(1): 1-9.
3. "PrimAry Angle-Closure Glaucoma-an Update." In *The 15th Congress of the Asia-Pacific Academy of Ophthalmology, Hong Kong, 1995; 03: 06-03, 10.*
4. Chen MJ. Normal tension glaucoma in Asia: Epidemiology, pathogenesis, diagnosis, and management. Taiwan Journal of Ophthalmology, 2020; 1, 10(4): 250-4.

5. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology, 2014; 1, 121(11): 2081-90.
6. Anderson DR, Drance SM, Schulzer M. NATURAL HISTORY, NORMAL TENSION GLAUCOMA. Journal of Glaucoma, 1999; 1, 8(1): S10.
7. Wiggs JL, Yaspan BL, Hauser MA, Kang JH, Allingham RR, Olson LM, Abdrabou W, Fan BJ, Wang DY, Brodeur W, Budenz DL. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. PLoS genetics, 2012; 26, 8(4): e1002654.
8. Allingham RR, Liu Y, Rhee DJ. The genetics of primary open-angle glaucoma: a review. Experimental eye research, 2009; 30, 88(4): 837-44.
9. Weisschuh N, Neumann D, Wolf C, Wissinger B, Gramer E. Prevalence of myocilin and optineurin sequence variants in German normal tension glaucoma patients. Mol Vis, 2005; 18, 11: 284-7.
10. Weisschuh N, Wolf C, Wissinger B, Gramer E. Variations in the WDR36 gene in German patients with normal tension glaucoma. Molecular vision, 2007; 13: 724.
11. Trivli A, Koliarakis I, Terzidou C, Goulielmos GN, Siganos CS, Spandidos DA, Dalianis G, Detorakis ET. Normal-tension glaucoma: Pathogenesis and genetics. Experimental and therapeutic medicine, 2019; 1, 17(1): 563-74.
12. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. British journal of ophthalmology, 2002; 1, 86(2): 238-42.
13. Wiggs JL, Pasquale LR. Genetics of glaucoma. Human molecular genetics, 2017; 1, 26(R1): R21-7.
14. Wang R, Wiggs JL. Common and rare genetic risk factors for glaucoma. Cold Spring Harbor perspectives in medicine, 2014; 1, 4(12): a017244.
15. Netland PA, Wiggs JL, Dreyer EB. Inheritance of glaucoma and genetic counseling of glaucoma patients. International ophthalmology clinics, 1993; 1, 33(2): 101-20.
16. Wood JM, Swann PG, Stavrou EP. Visual fields in glaucoma: a clinical overview. Clinical and Experimental Optometry, 2000; 83(3): 128-35.
17. Brusini P, Salvetat ML, Zeppieri M. How to measure intraocular pressure: an updated review of various tonometers. Journal of clinical medicine, 2021; 27, 10(17): 3860.

18. Chang DS, Xu L, Boland MV, Friedman DS. Accuracy of pupil assessment for the detection of glaucoma: a systematic review and meta-analysis. Ophthalmology, 2013; 1, 120(11): 2217-25.
19. Pillunat KR, Waibel S, Spoerl E, Herber R, Pillunat LE. Comparison of central corneal thickness measurements using optical and ultrasound pachymetry in glaucoma patients and elderly and young controls. Journal of Glaucoma, 2019; 1, 28(6): 540-5.
20. Geevarghese A, Wollstein G, Ishikawa H, Schuman JS. Optical coherence tomography and glaucoma. Annual review of vision science, 2021; 15, 7(1): 693-726.
21. Potop V, Coviltir V, Schmitzer S, Dragosloveanu CD, Ionescu CI, Burcel MG, Corbu MC, Dăscălescu DM. Ultrasound biomicroscopy in glaucoma assessment. Romanian Journal of Ophthalmology, 2021; 65(2): 114.
22. Weinreb RN, Zangwill L, Berry CC, Bathija R, Sample PA. Detection of glaucoma with scanning laser polarimetry. Archives of ophthalmology, 1998; 1, 116(12): 1583-9.
23. Schnyder A, Huwyler J. Drug transport to brain with targeted liposomes. NeuroRx, 2005; 2: 99-107.
24. Zarbin MA, Montemagno C, Leary JF, Ritch R. Nanotechnology in ophthalmology. Canadian Journal of Ophthalmology, 2010; 1, 45(5): 457-76.
25. Zarbin MA, Montemagno C, Leary JF, Ritch R. Nanomedicine in ophthalmology: the new frontier. American journal of ophthalmology, 2010; 1, 150(2): 144-62.
26. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. Jama, 2014; 14, 311(18): 1901-11.
27. Kim HJ, Zhang K, Moore L, Ho D. Diamond nanogel-embedded contact lenses mediate lysozyme-dependent therapeutic release. ACS nano, 2014; 25, 8(3): 2998-3005.
28. Goyal G, Garg T, Rath G, Goyal A. Current nanotechnological strategies for treating glaucoma. Critical Reviews™ in Therapeutic Drug Carrier Systems, 2014; 31(5).
29. Pita-Thomas DW, Goldberg JL. Nanotechnology and glaucoma: little particles for a big disease. Current opinion in ophthalmology, 2013; 1, 24(2): 130-5.
30. Zhu S, Gong L, Li Y, Xu H, Gu Z, Zhao Y. Safety assessment of nanomaterials to eyes: an important but neglected issue. Advanced Science, 2019; 6(16): 1802289.
31. Mastrobattista E, Koning GA, van Bloois L, Filipe AC, Jiskoot W, Storm G. Functional characterization of an endosome-disruptive peptide and its application in cytosolic delivery of immunoliposome-entrapped proteins. Journal of Biological Chemistry, 2002; 26, 277(30): 27135-43.

32. Urtti A, Hamalainen KM, Kananen K, Auriola S, Kontturi K. Characterization of Paracellular and Aqueous Penetration Routes in Cornea. Conjunctiva, and Sclera. investigative Ophthalmology & Visual Science, 1997; 38(3): 627-34.
33. Mehanna MM, Elmaradny HA, Samaha MW. Mucoadhesive liposomes as ocular delivery system: physical, microbiological, and in vivo assessment. Drug development and industrial pharmacy, 2010; 1, 36(1): 108-18.
34. Kouchak M, Bahmandar R, Bavarsad N, Farrahi F. Ocular Dorzolamide Nanoliposomes for Prolonged IOP Reduction: in-vitroand in-vivo Evaluation in Rabbits. Iranian journal of pharmaceutical research: IJPR, 2016; 15(1): 205.
35. Wong TT, Novack GD, Natarajan JV, Ho CL, Htoon HM, Venkatraman SS. Nanomedicine for glaucoma: sustained release latanoprost offers a new therapeutic option with substantial benefits over eyedrops. Drug delivery and translational research, 2014; 4: 303-9.
36. Mahale NB, Thakkar PD, Mali RG, Walunj DR, Chaudhari SR. Niosomes: novel sustained release nonionic stable vesicular systems—an overview. Advances in colloid and interface science, 2012; 15, 183: 46-54.
37. Liu G, Molas M, Grossmann GA, Pasumarthy M, Perales JC, Cooper MJ, Hanson RW. Biological properties of poly-l-lysine-DNA complexes generated by cooperative binding of the polycation* 210. Journal of Biological Chemistry, 2001; 14, 276(37): 34379-87.
38. Vandamme TF, Brobeck L. Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. Journal of controlled release, 2005; 20, 102(1): 23-38.
39. Weinreb RN, Caldwell DR, Goode SM, Horwitz BL, Laibovitz R, Shrader CE, Stewart RH, Williams AT. A double-masked three-month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution. American journal of ophthalmology, 1990; 1, 110(2): 189-92.
40. Rodriguez-Aller M, Guinchard S, Guillarme D, Pupier M, Jeannerat D, Rivara-Minten E, Veuthey JL, Gurny R. New prostaglandin analog formulation for glaucoma treatment containing cyclodextrins for improved stability, solubility and ocular tolerance. European Journal of Pharmaceutics and Biopharmaceutics, 2015; 1, 95: 203-14.
41. Tuomela A, Liu P, Puranen J, Rönkkö S, Laaksonen T, Kalesnykas G, Oksala O, Ilkka J, Laru J, Järvinen K, Hirvonen J. Brinzolamide nanocrystal formulations for ophthalmic delivery: reduction of elevated intraocular pressure in vivo. International journal of pharmaceutics, 2014; 5, 467(1-2): 34-41.

42. Zhou X, Rong R, Liang G, Li H, You M, Zeng Z, Xiao H, Ji D, Xia X. Simultaneously deplete reactive oxygen species and inhibit pyroptosis by dopamine/thioketal-containing polymers delivering disulfiram in combination with Cu (II) for acute glaucoma. Nano Today, 2022; 1, 47: 101668.
43. Iqbal H, Razzaq A, Zhou D, Lou J, Xiao R, Lin F, Liang Y. Nanomedicine in glaucoma treatment; Current challenges and future perspectives. Materials Today Bio, 2024; 4: 101229.