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REVIEW

Therapeutic Potential of Tocopherol and Tocotrienol in Glaucoma Management

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Abstract: Glaucoma is a leading cause of irreversible blindness worldwide, primarily driven by progressive optic nerve damage often associated with elevated intraocular pressure (IOP). While conventional treatments aim to reduce IOP, they fail to address the neurodegenerative mechanisms and oxidative stress underlying disease progression. This review evaluates the therapeutic potential of vitamin E isoforms which mainly focuses on tocopherol and tocotrienol. A comprehensive literature search on PUBMED following PRISMA guidelines identified 35 relevant studies published between 1950 and October 2024. These studies include clinical trials, in vivo, and in vitro investigations focusing on the antioxidant, neuroprotective, and IOP-modulating effects of tocopherol and tocotrienol. Tocopherol, especially α-tocopherol, has shown mixed clinical efficacy but consistent support for enhancing ocular blood flow and retinal ganglion cell survival. Tocotrienol, despite lower bioavailability, demonstrates superior antioxidant activity and potential for targeted neuroprotection. Advancements in drug delivery systems, including nanoliposomes, nanoparticles, and contact lenses, have further enhanced the ocular bioavailability of these compounds. However, the current evidence remains limited, with only a small number of clinical studies and inconsistent outcomes reported. This highlights an important opportunity for future research to focus on well-designed, longitudinal clinical trials that can better elucidate the therapeutic potential and clinical relevance of tocopherol and tocotrienol in glaucoma management. This review may provide an initial brief idea on the integration of vitamin E derivatives as adjunctive therapies in glaucoma management toward neuroprotection and oxidative stress mitigation.

Keywords: vitamin E, tocopherol, tocotrienol, glaucoma, antioxidants, intraocular pressure

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide, characterized by progressive optic nerve damage that often results from elevated intraocular pressure (IOP). The underlying pathology of glaucoma is largely attributed to impaired aqueous humor drainage, primarily through the trabecular meshwork and Schlemm's canal, leading to increased IOP.[1] This elevated pressure exerts mechanical stress on the optic nerve, compromising its blood supply and resulting in retinal ganglion cell (RGC) apoptosis, a hallmark of glaucoma-induced vision loss.[2]

Global projections of glaucoma prevalence have been reported in two landmark studies,[3,4] both demonstrating a steady increase over time (Figure 1). Global projections indicate a steady rise in glaucoma prevalence worldwide (Table 1). In 2010, approximately 60 million individuals were affected, increasing to nearly 80 million by 2020, with estimates suggesting more than 110 million cases by 2040.[4] The burden is highest in Africa and Asia, where limited access to early detection and treatment contributes to late-stage diagnosis. Primary open-angle glaucoma (POAG) remains the predominant form globally,[1,5] whereas primary angle-closure glaucoma (PACG) is more prevalent in Asian populations due to anatomical predisposition.[6] Despite IOP-lowering therapy, disease progression may persist in certain patients, as reported by Naik et al[7] who observed that a subset of individuals continued to worsen despite treatment. This therapeutic gap underscores the need for adjunctive approaches targeting neurodegeneration and oxidative stress, the two molecular pathways through vitamin E derivatives, particularly tocopherols and tocotrienols, may exert beneficial effects.

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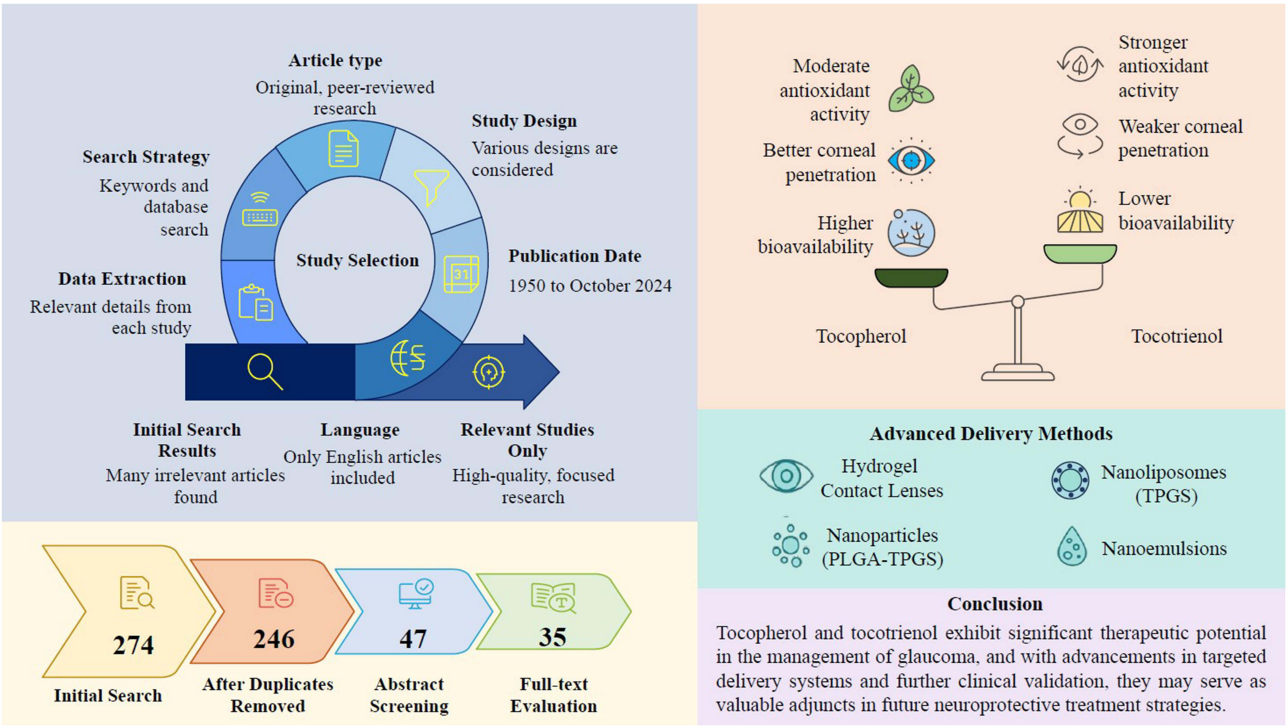
Graphical Abstract



The socioeconomic impact of glaucoma is profound Figure 2, as vision impairment leads to reduced quality of life, increased healthcare costs, and a growing burden on caregivers and public health systems.[9] Current glaucoma management primarily focuses on lowering IOP through pharmacological agents, laser therapy, or surgical interventions. However, these approaches do not directly address the neurodegenerative aspect of the disease or the oxidative stress-induced damage to RGCs, which ultimately leads to vision loss.[10] A significant limitation of this IOP-centric approach is that glaucomatous damage can continue even when IOP is within the normal range, indicating the involvement of

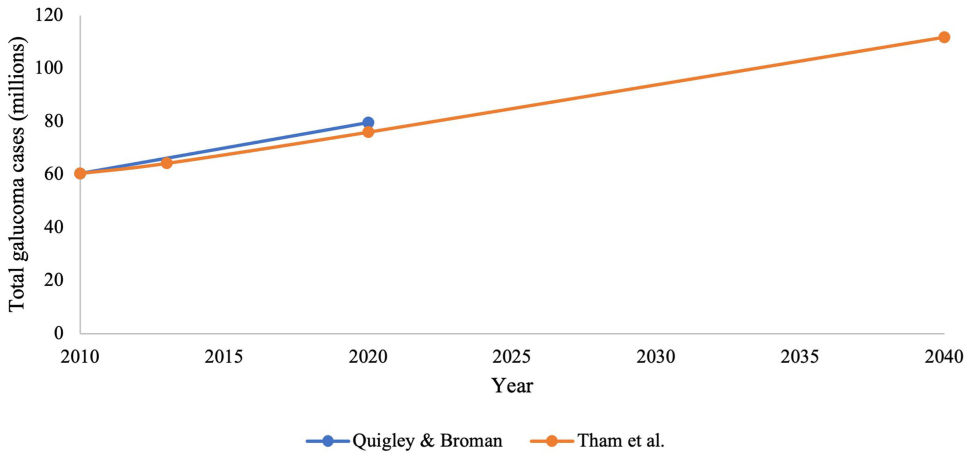


Figure 1 Worldwide Glaucoma Projection.

Table 1 Estimated Glaucoma Cases

Continent	Estimated Glaucoma Cases (Millions)	Year	Types of Glaucoma	Reference
Asia	39.00 36.89	2013 2020	POAG and PACG POAG	Tham et al[4] Zhang et al[8]
Africa	8.29 10.68	2013 2020	High POAG prevalence POAG	Tham et al[4] Zhang et al[8]
Europe	6.77 9.21	2013 2020	High POAG prevalence POAG	Tham et al[4] Zhang et al[8]
North America	3.36 6.04	2013 2020	High POAG prevalence POAG	Tham et al[4] Zhang et al[8]
South America	6.59 3.90	2013 2020	POAG and PACG POAG	Tham et al[4] Zhang et al[8]
Oceania	0.2–0.31	2013 and 2020	High POAG prevalence	Tham et al[4] Zhang et al[8]
World	64.26 68.56	2013 2020	POAG and PACG POAG	Tham et al[4] Zhang et al[8]

additional pathological mechanisms. One of the most critical of these mechanisms is oxidative stress, which plays a key role in the pathophysiology of glaucoma.

Oxidative stress plays a central role in the cascade of molecular events leading to axonal degeneration and RGCs loss in glaucoma, as illustrated in Figure 3. It disrupts mitochondrial function, triggers neuroinflammation, and promotes the

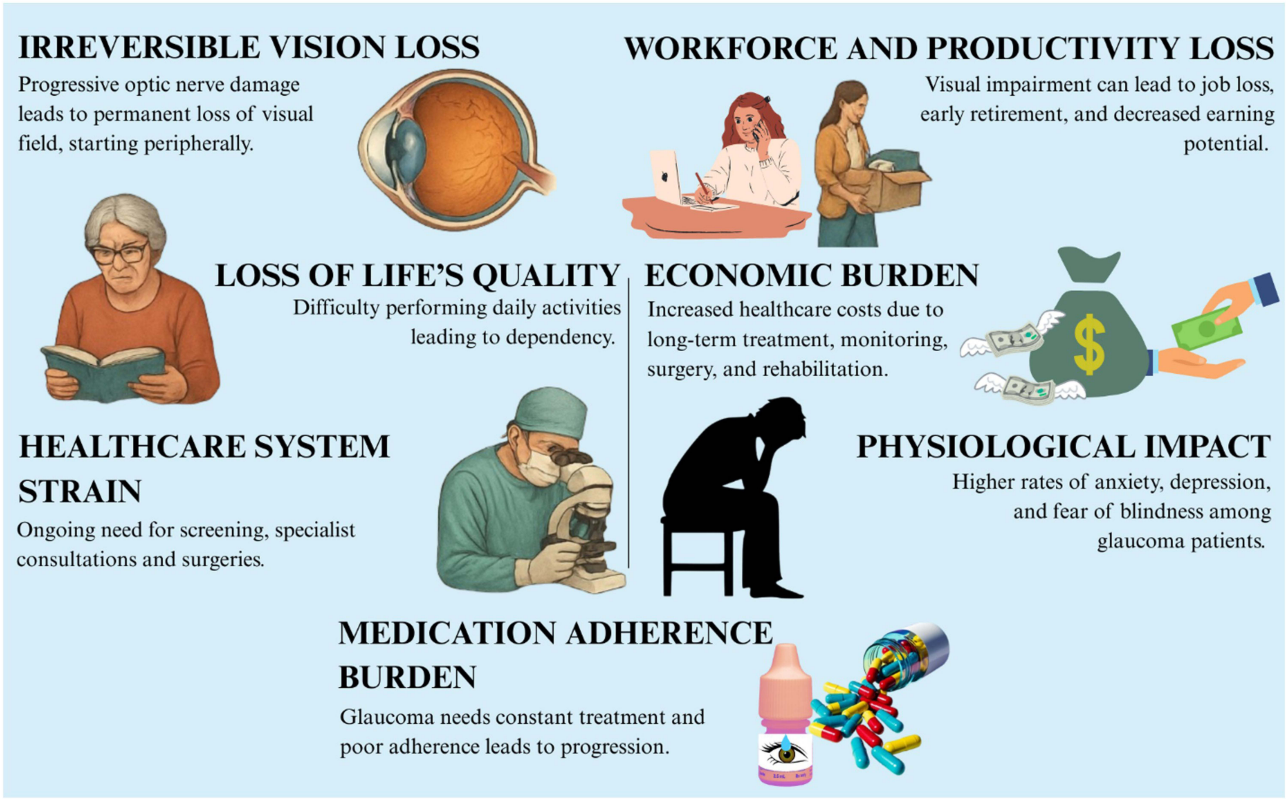


Figure 2 Burden and effects of Glaucoma.[11]
Note: Figure created using Canva.

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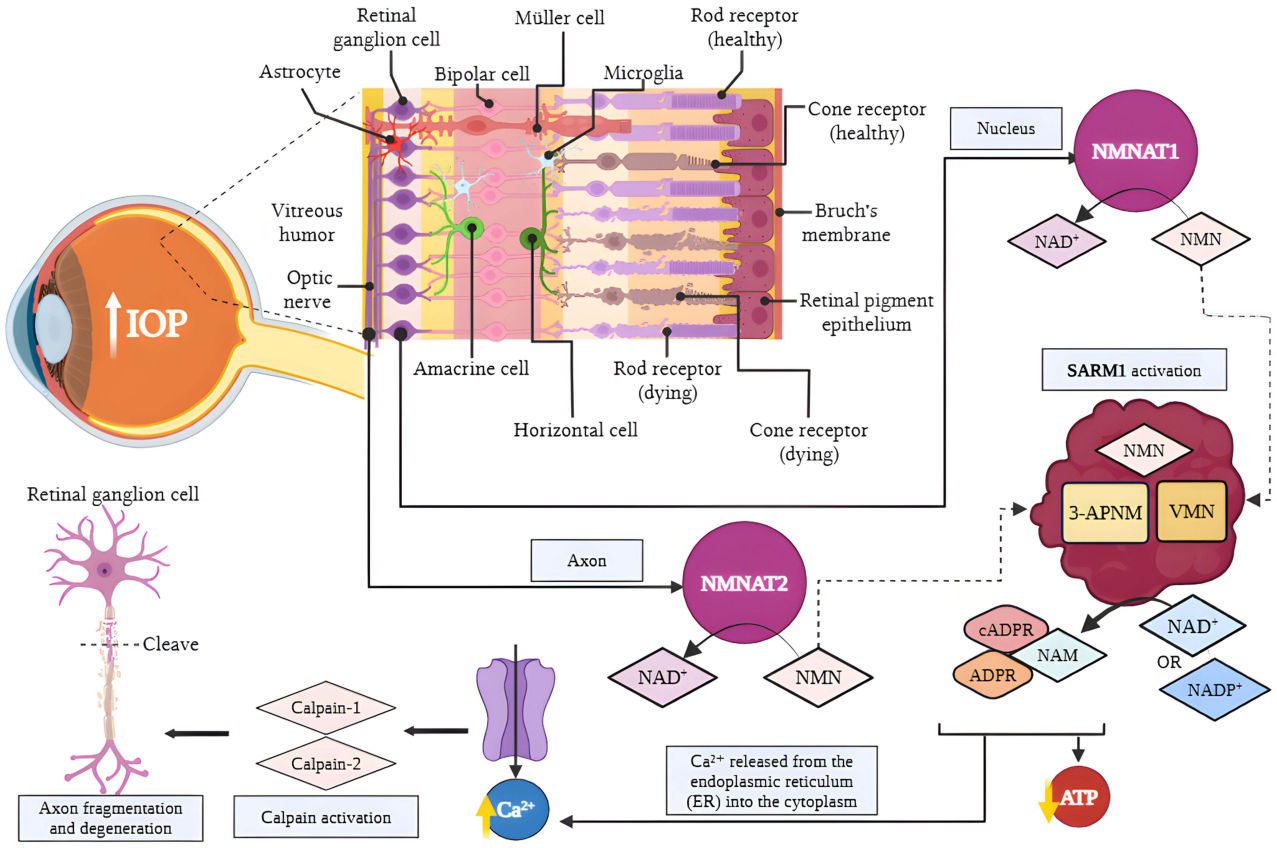

Figure 3 This figure illustrates the sequential molecular events leading to axonal degeneration and retinal ganglion cell (RGC) loss in glaucoma.
Notes: Elevated intraocular pressure (IOP) induces mechanical stress at the optic nerve head (ONH) and lamina cribrosa, disrupting axonal transport in RGC axons. Loss of axonal NMNAT2 (Nicotinamide Mononucleotide Adenylyltransferase 2) results in NAD+ depletion and NMN (Nicotinamide Mononucleotide) accumulation, leading to activation of the pro-degenerative enzyme SARM1. While NMNAT1 (Nicotinamide Mononucleotide Adenylyltransferase 1), located in the nucleus, continues to synthesize NAD+, it lacks the capacity to protect axons due to its nuclear localization and absence of axonal projections (short axon). NMNAT1 also become insufficient to support nuclear NAD+ demand, especially under prolonged stress, contributing to nuclear dysfunction or degeneration. As NMN accumulates, it activates SARM1, which degrades NAD+ into NAM (Nicotinamide), ADP-ribose (ADPR), and cyclic ADP-ribose (cADPR). These metabolites (cADPR and ADPR) triggers calcium (Ca^{2}+) release from the endoplasmic reticulum (ER). Elevated cytosolic Ca^{2}+ levels activate calpains, which cleave the axonal structural proteins. As a result, causes cytoskeletal destabilization, degrade axonal structural proteins, disrupt mitochondrial function, and irreversible axon fragmentation. Symbols: yellow arrow ↑ = elevation/increase; yellow arrow ↓ = reduction/decrease; black arrow → = process flow or signalling direction. This figure adapted from Loreto, Merlini & Coleman[13] and Tarasiuk et al[14] and recreated using BioRender.com.

apoptosis of RGCs. While IOP control remains a fundamental aspect of treatment, the persistent progression of glaucoma highlights a pressing need to explore complementary therapeutic strategies that target these underlying neurodegenerative processes. In this context, antioxidants have emerged as promising candidates due to their ability to counteract oxidative stress, a critical factor in the pathophysiology of glaucoma.[12] Among the various antioxidants explored, vitamin E, comprising tocopherols and tocotrienols, has gained considerable attention for its potential therapeutic role in neuroprotection and ocular health.

Emerging evidence suggests that vitamin E supplementation may play a crucial role in preserving RGCs, reducing oxidative stress, and potentially lowering IOP.[15] Tocopherols and tocotrienols, the two major forms of vitamin E (Figure 4), are lipid-soluble compounds with potent antioxidant properties. Tocopherol, particularly α-tocopherol, has been extensively studied for its ability to inhibit lipid peroxidation, stabilize cell membranes, and modulate inflammatory pathways.[16]

Based on Figure 5, Tocopherols have been shown to protect retinal tissues by neutralizing free radicals, preventing lipid peroxidation, and maintaining mitochondrial integrity.[18] Tocotrienols, on the other hand, demonstrate superior neuroprotective effects by modulating key signaling pathways involved in neuronal survival and apoptosis.[19] Meanwhile, tocotrienols exhibit superior antioxidant activity due to their unsaturated isoprenoid side chains, allowing for better membrane penetration

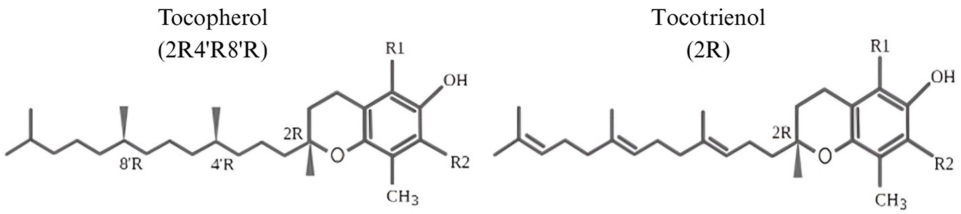

Figure 4 Structures of tocopherol and tocotrienol and their metabolites retrieved from Brigelius-Flohé.[17]
Note: Recreated with BioRender.com.

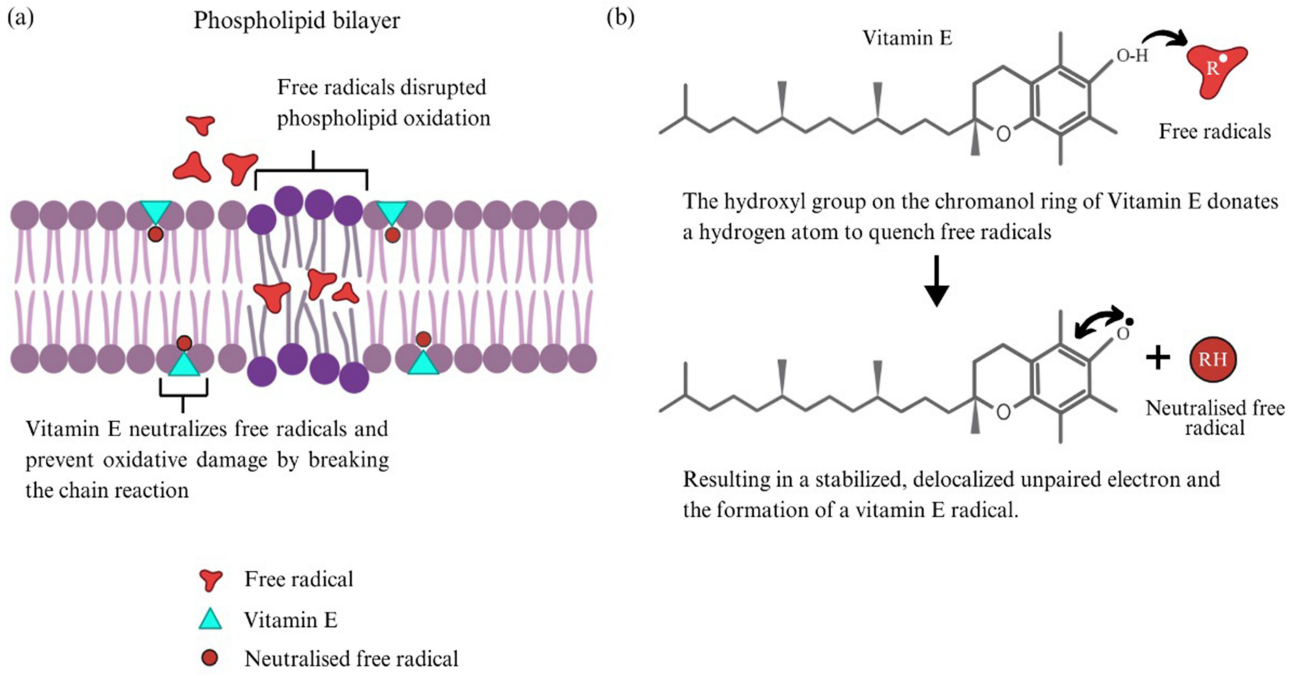

Figure 5 (**a**) The role of vitamin E as an antioxidant in cell membranes. (**b**) The vitamin E structure relationship in scavenging free radicals by donating hydrogen atoms.
Notes: (**a**) Recreated from Knight et al[23] (**b**) adapted from Rungratanawanich et al[24] and reconstructed using BioRender.com.

and free radical scavenging.[20] This structural advantage endows tocotrienols with enhanced neuroprotective, anti-inflammatory, and anti-angiogenic properties, making them promising candidates for glaucoma management.[21,22]

Beyond glaucoma, vitamin E has been implicated in the management of other ocular degenerative conditions, such as cataracts and diabetic retinopathy. Both tocopherols and tocotrienols have demonstrated protective effects against cataractogenesis by reducing oxidative and nitrosative stress, inhibiting NF-κB activation, and preventing glucocorticoid-induced cataract formation.[25,26] In diabetic retinopathy, tocopherols mitigate oxidative stress and inhibit angiogenesis, while tocotrienols suppress inflammatory pathways by downregulating vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1), thereby preserving retinal structure and function.[27,28]

This review aims to critically evaluate existing literature on the role of vitamin E in glaucoma, with a specific focus on its therapeutic potential in mitigating oxidative stress, preserving RGCs, and regulating IOP. By synthesizing current findings, this review will highlight the potential clinical applications of tocopherols and tocotrienols, providing a foundation for future research and therapeutic advancements in glaucoma care.

Method of Literature Search

The review was conducted in accordance with a predefined protocol and the standardized guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[29]

Inclusion and Exclusion Criteria

The inclusion criteria for the studies were established as follows: (1) article published in English language, (2) Only studies published from 1950 onward, and October 2024 were considered, (3) Evaluating the association between glaucoma and vitamin E (Tocopherol and Tocotrienol) in a clinical study, preclinical study, prospective study, randomized controlled trial, case-control study, or cross-sectional study.

The inclusion criteria were established to ensure the relevance, reliability, and comprehensiveness of the selected studies. Only articles published in the English language were included to maintain consistency in interpretation and to avoid potential inaccuracies due to translation issues. The publication range from 1950 to October 2024 was selected to encompass both foundational and contemporary research, as studies on vitamin E particularly tocopherol, the first form of vitamin E to be discovered, became more prominent in scientific literature from the early 1950s onward. Furthermore, the inclusion of various study designs such as clinical studies, preclinical studies, prospective studies, randomized controlled trials, case-control studies, and cross-sectional studies allowed for a comprehensive evaluation of the association between glaucoma and vitamin E (Tocopherol and Tocotrienol), integrating both mechanistic insights and clinical relevance.

In contrast, studies or papers that are irrelevant with the predefined inclusion criteria were systematically excluded. The criteria of exclusion studies were: (1) Study protocols, literature review, methodological papers or conference abstracts were excluded, (2) Article review, mini-review, meta-analysis, systematic review, (3) Published studies in other than English language. In contrast, studies or papers that did not meet the predefined inclusion criteria were systematically excluded to ensure the relevance and quality of the review.

Search Strategy

The systematic search on this literature was conducted up to October 1st, 2024. Additionally, reference lists of identified articles were reviewed to include studies that contain relevant keywords or keyword combinations. The PubMed database search employed the following keywords or MeSH (Medical Subject Headings) terms: Tocopherol AND glaucoma; Tocotrienol AND glaucoma; Tocopherol AND retina; Tocotrienol AND retina; Vitamin E AND glaucoma. PubMed was chosen as it is a free resource for searching and retrieving literature focused on biomedical and life sciences.

The search results were exported into Endnote X9 for effective citation management and deduplication. The subsequent screening process was conducted using Rayyan QCRI (Qatar Computing Research Institute) Intelligent Systematic Review, a web-based tool designed to facilitate systematic reviews. This platform enabled the screening of abstracts and full-text articles based on pre-established inclusion and exclusion criteria. After removing duplicates, studies were screened by title and abstract based on the predefined inclusion and exclusion criteria. Articles with uncertain eligibility underwent full-text evaluation, and the reference lists of included studies were manually reviewed to identify additional relevant publications. Three independent reviewers conducted the screening, and any discrepancies were resolved through discussion and consensus.

Data Extraction

The following details were extracted from each study included in the review:

1. Citation information (title of the article, first author name and the year of publication)
2. Study design
3. Sample size
4. Type of compound(s)
5. Route of administration
6. Main findings.

Result

The PubMed database yielded 274 articles in total during the initial search process. After the removal of duplicate entries, 246 articles remained, which were subsequently screened and evaluated against the predetermined inclusion and exclusion criteria. From these, 199 were excluded (Article review, mini-review, meta-analysis, systematic review; Published studies in languages other than English; irrelevant to glaucoma background studies; wrong compound used). Figure 6 shows the study selection process.

Following the abstract screening, a full-text evaluation was performed for 47 studies. After a thorough analysis, 12 studies were excluded due to the fact that, they did not specifically address the association between glaucoma and vitamin E treatment. Instead, these studies focused on biomarkers of vitamin E in glaucoma and other related conditions. As a result, this review consists of 35 studies that were considered relevant according to the predetermined criteria.

Figure 6 provides an overview of the main characteristics of the included studies. It was observed that most of the research investigating the relationship between vitamin E and glaucoma were published in 2007, followed by a smaller peak in the 90s. The included studies utilized a variety of study designs, with in vivo (n = 9) and in vitro (n = 9) being the most common. Additionally, two studies incorporated a combination of in vivo, in vitro, and ex vivo approaches, while three studies employed both in vivo and in vitro methods. A total of 12 studies were clinical, randomized trials, case studies and observational studies.

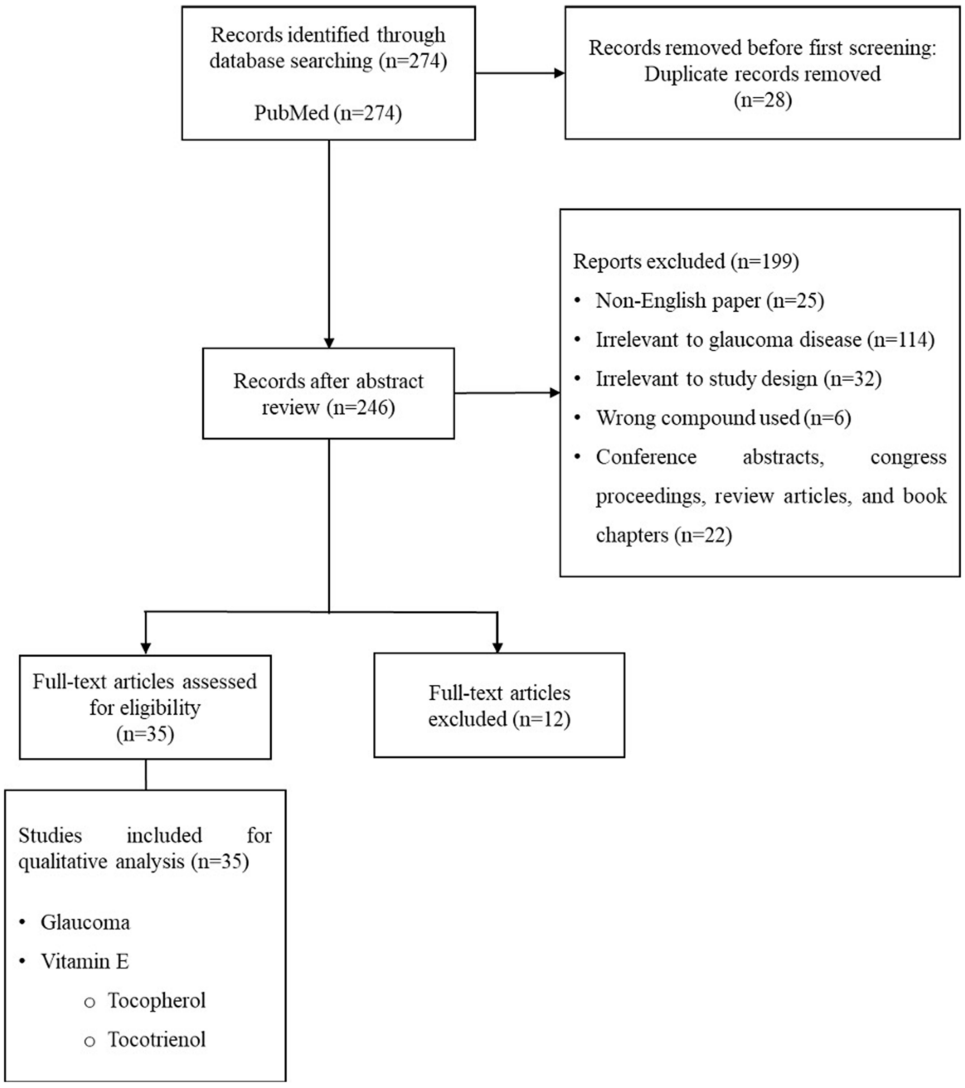

Figure 6 Review flow diagram.

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Regarding the forms of vitamin E assessed, 80% of the studies focused on Tocopherol alone and 20% investigated both Tocopherol and Tocotrienol (vitamin E). Out of the 35 included studies, 17 (47.22%) directly addressed the management of glaucoma, while the remaining 18 studies (51.43%) primarily investigated neuroprotection (Table 2). Although these neuroprotection studies did not directly target glaucoma, they provided valuable insights into retinal health preservation, a critical factor in preventing and managing glaucoma.

As this work is a narrative systematic review, no new experimental data were generated, and therefore, no statistical or meta-analytical analysis was performed. The findings presented herein are based on a qualitative synthesis of relevant

Table 2 Compilations of Clinical, Prospective, Case Studies, or Reports, In Vitro and In Vivo Studies of Tocopherol and Tocotrienol

Vitamin E Type	Dose & Route of Administration	Target Population & Study Type	Glaucoma Parameter Findings	Antioxidant Markers & Findings	Reference
Human/Clinical Studies					
α- and γ-tocopherol	Dietary/supplemental	Genetic database (MR study)	No changes in IOP, mRNFL, mGCIPL	N/A	Xiong et al[30]
α-tocopherol acetate	300 and 600 mg/day orally	30 glaucomatous patients; RCT	PI & RI ↓; VF improvement	N/A	Engin et al[31]
α-tocopherol acetate	300 mg/day orally for 2 months	41 POAG/pseudo-exfoliative glaucoma patients; RCT	IOP ↓ at 2 weeks/months; no effect on surgery success	N/A	Goldblum et al[32]
Vitamin E TPGS (500 mg) + CoQ10 (100 mg)	Topical	43 OAG patients; case study	PERG amplitude ↑, implicit time ↓	N/A	Parisi et al[33]
Vitamin E TPGS (500 mg) + CoQ10 (100 mg)	Topical	72 patients (PEG, PEX); RCT	SOD ↑ in PEG+Coqun; MDA unchanged	SOD ↑ ($p<0.05$); MDA no change	Ozates et al[34]
α-tocopherol acetate	Oral (dose not stated) + citicoline and homotaurine	NTG patient (38F); case report	VF improved; RNFL & GC stabilized	N/A	Verdina et al[35]
Vitamin E (12 mg) + citicoline + homotaurine	Oral	109 POAG patients; multicenter RCT	CS and QoL ↑; no VF change	N/A	Marino et al[36]
α- and γ-tocopherol	Dietary supplements	2912 participants >40 y; NHANES	No clear link between serum Vit E and glaucoma	N/A	Wang et al[37]
α-tocopherol (600 mg/day)	Oral	30 adults; observational	IOP increase after eyelid closure ↓	N/A	Pescosolido et al[38]
Vitamin E (with B-vitamins and DHA)	Oral (Trofinerv)	30 glaucoma patients; case report	VF & contrast sensitivity improved	N/A	Cellini et al[39]
Vitamin E (dietary)	Dietary intake	18,669 participants; cohort study	No link with glaucoma risk	N/A	Moreno-Montañés et al[40]
Vitamin E (dietary)	Dietary intake	116,484 participants; NHS & HPFS cohort	No association with POAG risk	N/A	Kang et al[41]

(*Continued*)

Table 2 (Continued).

Vitamin E Type	Dose & Route of Administration	Target Population & Study Type	Glaucoma Parameter Findings	Antioxidant Markers & Findings	Reference
In Vitro and In Vivo Studies					
α-tocopherol acetate / succinate	100 mg; subconjunctival	Rabbits; In vivo	IOP ↓ from ~22 to ~15 mmHg by day 7–30	N/A	Pinilla et al[42]
Trolox (α-tocopherol analogue)	10 μM orally	RGC-5 cells and mice; In vitro + In vivo	↓ TUNEL+ cells, retinal protection	↓ 4-HNE, ↑ cell viability	Nakajima et al[43]
Vit E-TPGS	Topical (nanoparticles)	Rabbits; In vivo + Ex vivo	IOP ↓ up to 29.1%, sustained up to 20h	N/A	Warsi et al[44]
D-α-tocopherol	Contact lens delivery	Beagle dogs; In vivo	IOP ↓ 3–5 mmHg; PS ↓ significantly	N/A	Peng et al[45]
TPGS + Brimonidine	Topical drops	Rabbits; In vivo + Ex vivo	IOP ↓ 34.5%, sustained for 8 h	N/A	Sharma & Chauhan[46]
Vit E + CoQ10	Topical	Wistar rats; In vivo	↑ RGC survival, ↓ GFAP	N/A	Ekicier Acar et al[47]
α-tocopherol	Subcutaneous	Rats (I/R model); In vivo	↓ MDA; ↑ GSH	↓ MDA ($p<0.01$), ↑ GSH ($p<0.001$)	Dilsiz et al[48]
α-/γ-tocopherol, TPGS	Subcutaneous	Guinea pigs; In vivo	↑ inner plexiform layer thickness	N/A	Aydemir et al[49]
α-tocopherol	Intraperitoneal	Guinea pigs; In vivo	↓ MDA, ↑ IPL thickness	↓ MDA ($p<0.01$)	Demir et al[50]
α-tocopheryl acetate (natural/synthetic)	Dietary	Wistar rats; In vivo	↑ ERG, ↓ latency; VEP stable	↑ Vit E in tissue; ↓ liver MDA	Hayton et al[51]
CoQ10 + TPGS micelles	Topical	Rats & retinal cultures; In vivo + In vitro	↓ RGC apoptosis	↓ ROS; TPGS alone not effective	Davis et al[52]
TPGS nanoliposomes + Brz	Topical	Rabbits; In vivo	IOP ↓ up to 35.2%, effect lasted 11 h	N/A	Jin et al[53]
α-tocopherol	Direct (0.5–8 mM)	Retinal tissue; In vitro	↑ Cell viability; ↓ ROS	↓ ROS ($p<0.001$)	Lee et al[54]
α-tocopherol + Zeaxanthin	Direct	ARPE-19 cells; In vitro	↑ Survival after irradiation	N/A	Różanowska et al[55]
α-tocopherol-HDL	Direct	TR-iBRB2 (rat endothelial cells); In vitro	Active uptake via SR-BI	N/A	Tachikawa et al[56]
α-tocopherol + antifibrotics	Direct	Human fibroblasts; In vitro	↓ cytotoxicity with paclitaxel/MMC/5FU	N/A	Engin et al[57]
α-tocopherol	Direct	Dog retina tissue; In vitro	↓ TBARS; DHA preserved	↓ TBARS, ↑ DHA ($p<0.05$)	Zapata et al[58]
d-α-tocopherol	50–100 μM; direct	Human Tenon fibroblasts; In vitro	↓ Cell proliferation (60–77%)	N/A	Haas et al[59]
Vitamin E	10–100 μM; direct	Human TM cells; In vitro	↓ αβ-crystallin and fibronectin ($p<0.05$)	↓ TGF-β2-induced oxidative markers	Yu et al[60]

(*Continued*)

Table 2 (Continued).

Vitamin E Type	Dose & Route of Administration	Target Population & Study Type	Glaucoma Parameter Findings	Antioxidant Markers & Findings	Reference
Vitamin E succinate/ acetate	5–80 mM; direct	Chick retinal cells; In vitro	↓ LDH, ↓ ATP:ADP at high dose	↓ TBARS	Rego et al[61]
Vitamin E (dietary)	Supplemented feed	Wistar rats; In vivo	DE group: ↓ RGCs, ↑ peroxidation	↑ serum Vit E; SOD/ GSH/catalase unchanged	Ko et al[62]
α-/γ-tocopherol, tocotrienol	Topical & oral	Wistar rats; In vivo	↑ ocular bioavailability with Toc-3	N/A	Tanito et al[63]
Vitamin E	200 μM; direct	Human GTM/NTM cells; In vitro	↓ ROS in glaucoma TM cells	↓ ROT-induced ROS ($p<0.05$)	He et al[64]

Notes: Symbols: arrow ↑ = elevation/increase; arrow ↓ = reduction/decrease.
Abbreviations: Vit E, Vitamin E; TPGS, D-α-Tocopheryl Polyethylene Glycol 1000 Succinate; CoQ10, Coenzyme Q10; RCT, Randomized Controlled Trial; MR, Mendelian Randomization; VF, Visual Field; IOP, Intraocular Pressure; PERG, Pattern Electroretinogram; RNFL, Retinal Nerve Fiber Layer; mRNFL, Mean Retinal Nerve Fiber Layer; mGCIPL, Mean Ganglion Cell–Inner Plexiform Layer; NTG, Normal Tension Glaucoma; POAG, Primary Open-Angle Glaucoma; PEG, Pigmentary Glaucoma; PEX, Pseudoexfoliation Glaucoma; CS, Contrast Sensitivity; QoL, Quality of Life; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; RGC, Retinal Ganglion Cells; GFAP, Glial Fibrillary Acidic Protein; IPL, Inner Plexiform Layer; ERG, Electroretinogram; VEP, Visual Evoked Potential; ROS, Reactive Oxygen Species; ARPE-19, Adult Retinal Pigment Epithelial Cells, Line 19; HDL, High-Density Lipoprotein; SR-BI, Scavenger Receptor Class B Type I; MMC, Mitomycin C; 5FU, 5-Fluorouracil; TBARS, Thiobarbituric Acid Reactive Substances; DHA, Docosahexaenoic Acid; TM, Trabecular Meshwork; GTM, Glaucomatous Trabecular Meshwork; NTM, Normal Trabecular Meshwork; TGF-β2, Transforming Growth Factor Beta 2; LDH, Lactate Dehydrogenase; ATP:ADP, Adenosine Triphosphate to Adenosine Diphosphate Ratio; DE, Diabetic Eye; Toc-3, Tocotrienol-rich Formulation; N/A, Not Applicable.

published studies, focusing on summarizing current evidence and identifying research gaps related to the therapeutic potential of tocopherol and tocotrienol in glaucoma management.

Tocopherol: Clinical, Prospective, Case Studies, or Reports

A study by Xiong et al[30] used Mendelian randomization to assess the genetic predisposition to tocopherol levels and their association with glaucoma-related traits. The findings showed no significant relationship between α-tocopherol or γ-tocopherol intake and changes in IOP, macular retinal nerve fiber layer (mRNFL) thickness, or macular ganglion cell–inner plexiform layer (mGCIPL) thickness. Similarly, a large-scale population-based study by Wang et al[37] found no conclusive association between supplemental Vitamin E intake and glaucoma prevalence. While unadjusted models suggested some protective effects at specific serum tocopherol levels, these effects disappeared after adjusting for confounding factors.

Several randomized controlled trials (RCTs) have explored the effects of oral tocopherol supplementation on IOP and ocular blood flow. Engin et al[31] conducted an RCT in glaucomatous patients, where oral α-tocopherol acetate at doses of 300 mg/day and 600 mg/day significantly improved ocular hemodynamics, reducing the pulsatility index (PI) and resistivity index (RI) in the ophthalmic and posterior ciliary arteries. Additionally, mean deviations in visual fields were significantly lower in supplemented groups compared to controls.

However, Goldblum et al[32] found no significant effect of oral α-tocopherol (300 mg/day for two months) on trabeculectomy or phacotrabeculectomy success rates, IOP reduction, or postoperative complications. These results suggest that while tocopherol may enhance ocular blood flow, its direct impact on surgical outcomes and long-term IOP regulation remains uncertain. An observational study by Pescosolido et al[38] supported the notion that Vitamin E supplementation (600 mg/day) could mitigate IOP spikes caused by the closed eyelid test (CET), indicating potential short-term benefits in IOP modulation.

Neuroprotective strategies in glaucoma management have also gained interest, with several studies examining topical formulations containing tocopherol. Parisi et al[33] investigated the combination of coenzyme Q10 and Vitamin E (Coqun) in patients with open-angle glaucoma (OAG). Their findings revealed significant improvements in pattern

electroretinogram (PERG) amplitudes and implicit times, suggesting enhanced retinal ganglion cell function. Similarly, Ozates et al[34] reported that Coqun-treated pseudo-exfoliative glaucoma (PEG) patients had significantly lower aqueous humor superoxide dismutase (SOD) levels, indicating an antioxidant effect, although malondialdehyde (MDA) levels remained unchanged.

Case studies have further explored tocopherol's potential role in glaucoma management. Verdina et al[35] reported that Vitamin E supplementation, combined with citicoline and homotaurine, improved visual field parameters and stabilized retinal nerve fiber layer (RNFL) thickness over a 30-month follow-up in a patient with normal-tension glaucoma (NTG). Similarly, Marino et al[36] conducted a multicenter pilot study on primary open-angle glaucoma (POAG) patients, examining a combination of Vitamin E, citicoline, and homotaurine. The study found improvements in contrast sensitivity and quality of life but no significant changes in visual field outcomes, suggesting a supportive rather than primary therapeutic role.

Tocopherol: in vivo and in vitro Studies

Several studies underscore the effectiveness of tocopherols in reducing IOP, a key factor in glaucoma management. Pinilla et al[42] demonstrated that α-tocopherol acetate (ATA) and α-tocopherol acid succinate (ATS) significantly reduced IOP in pigmented rabbits following subconjunctival injections. Similarly, Warsi et al[44] reported that vitamin E-TPGS nanoparticles enhanced the sustained release of dorzolamide, prolonging IOP reduction for up to 20 hours. These findings suggest that tocopherol-based formulations may offer more prolonged and effective therapeutic outcomes compared to conventional treatments.

Peng et al[45] further investigated vitamin E's role in enhancing drug delivery via contact lenses, demonstrating significant IOP reductions in beagle dogs. The incorporation of vitamin E into these lenses facilitated controlled and sustained drug release, which could be beneficial for glaucoma patients who struggle with frequent eye drop administration.

In addition to their role in IOP reduction, the neuroprotective properties of tocopherols have been well-documented. Nakajima et al[43] examined Trolox, a water-soluble derivative of α-tocopherol, in both in vitro and in vivo settings. Their study showed that Trolox effectively mitigated oxidative stress-induced retinal damage and improved cell viability, particularly when combined with coenzyme Q10 (CoQ10).

Ekicier Acar et al[47] provided further support for vitamin E's neuroprotective effects when co-administered with CoQ10 in Wistar rats with optic nerve injuries. The treatment significantly preserved Brn-3a-positive retinal ganglion cells (RGCs) and reduced glial fibrillary acidic protein (GFAP) expression, indicating lower neuroinflammation. These findings align with those of Davis et al[52] who observed that CoQ10/TPGS micelles reduced apoptosis and preserved RGC density in retinal cell cultures and rat models.

Ischemia-reperfusion (IR) injury is a major contributor to optic neuropathies, and several studies have investigated its mitigation through tocopherol treatment. Aydemir et al[49] found that α-tocopherol, γ-tocopherol, and TPGS significantly reduced lipid peroxidation while increasing glutathione (GSH) levels, suggesting enhanced antioxidant defense mechanisms. Similarly, Dilsiz et al[48] reported that vitamin E supplementation lowered MDA levels and restored GSH levels in IR-induced retinal damage models. Interestingly, study done by Demir et al[50] in a guinea pig model of experimental uveitis, α-tocopherol was shown to mitigated retinal oxidative injury induced by intravitreal injection of bovine serum albumin. Findings showed that α-tocopherol significantly reduced MDA levels and decreased the thickness of the inner plexiform layer, indicating reduced retinal edema and oxidative damage. Mechanistically, alpha-tocopherol acts as a free radical scavenger that interrupts lipid peroxidation chains in photoreceptor membranes, thereby stabilizing cell membranes and preserving retinal structure.

Hayton et al[51] examined the impact of dietary vitamin E intake on visual function and oxidative stress in Wistar rats. Their findings indicated that a vitamin E-deficient diet led to prolonged visual evoked potential (VEP) latencies and decreased electroretinogram (ERG) amplitudes, while supplementation preserved these visual responses. This highlights the systemic benefits of vitamin E beyond localized ocular administration.

Recent advancements in nanoformulations have significantly improved the bioavailability and efficacy of tocopherol-based treatments. Sharma & Chauhan[46] demonstrated that brimonidine tartrate (BRT) nanoparticles formulated with

PLGA-TPGS achieved greater IOP reduction compared to commercially available formulations. Similarly, Jin et al[53] observed superior IOP-lowering effects with TPGS nanoliposomes compared to conventional AZOPT® eye drops, emphasizing the potential of nanotechnology in ophthalmic drug delivery.

Lee et al[54] found that pretreatment with α-tocopherol significantly improved cell viability in retinal tissues exposed to oxidative injury, achieving neuroprotection at concentrations as low as 0.5 mM. Similarly, Różanowska et al[55] reported that α-tocopherol enhanced the survival of ARPE-19 cells under irradiation-induced stress, with even greater efficacy when combined with zeaxanthin. These findings suggest that tocopherol is a potent antioxidant capable of counteracting oxidative damage in the retina.

Understanding tocopherol's cellular uptake is crucial for determining its efficacy in retinal health. Tachikawa et al[56] investigated the uptake mechanisms of [14C]α-tocopherol-HDL by retinal capillary endothelial cells and found that uptake was temperature-dependent and mediated by the scavenger receptor SR-BI. This study underscored SR-BI's essential role in maintaining tocopherol levels in the neural retina, a mechanism vital for its neuroprotective function.

The combination of tocopherol with other therapeutic agents has shown promising results. Engin et al[57] examined its synergistic effects with paclitaxel, mitomycin C, and 5-FU, demonstrating reduced cytotoxicity and enhanced antifibrotic efficacy in human Tenon's fibroblasts. These findings suggest potential clinical applications of tocopherol in post-surgical ocular treatments to prevent fibrosis and improve healing outcomes.

Tocopherol's impact on lipid peroxidation was evident in a study by Zapata et al[58] which demonstrated its effectiveness in reducing lipid peroxidation in dog retinal tissues. The reduction in TBARS content and preservation of docosahexaenoic acid (DHA) further highlight tocopherol's role in maintaining retinal lipid integrity, which is crucial for photoreceptor function.

Yu et al[60] investigated vitamin E's role in modulating fibrotic markers in human trabecular meshwork cells, showing a significant reduction in TGF-β2-induced α-crystallin and fibronectin expression. These results suggest that tocopherol may help prevent fibrotic changes associated with glaucoma progression, offering a potential therapeutic avenue.

Tocopherol and Tocotrienol: Prospective and Case Studies

A large-scale prospective cohort study by Moreno-Montañés et al[40] investigated the dietary intake of vitamin E among 18,669 participants and found no significant association between vitamin E consumption and glaucoma risk (HR: 1.13, 95% CI: 0.84–1.52). Similarly, another extensive cohort study by Kang et al[41] which analyzed data from the Nurses' Health Study (n = 76,200) and the Health Professionals Follow-up Study (n = 40,284), reported no significant correlation between dietary vitamin E intake and POAG incidence (rate ratio: 0.97, 95% CI: 0.62–1.52). These findings suggest that dietary vitamin E alone may not be a key factor in glaucoma prevention, highlighting the need for further exploration of different formulations, dosages, and delivery mechanisms.

Although large-scale cohort studies did not establish a protective role for dietary vitamin E against glaucoma, a case study with long-term follow-up by Cellini et al[39] presented a contrasting perspective. In this study, 30 patients (aged 58–74 years) were given TROFINERV, a formulation containing polyunsaturated fatty acids (DHA and EPA), vitamin E, and B vitamins. After three months of therapy, all perimetric indices showed significant improvement ($p<0.05$ for mean defect [MD] and $p<0.05$ for corrected pattern standard deviation [CPSD]). Retinal contrast sensitivity (RCS) at medium-high frequencies improved after one month and extended to medium-low frequencies by the third month. These findings suggest that combining vitamin E with other neuroprotective compounds may enhance its therapeutic effects on glaucomatous optic neuropathy.

Tocopherol and Tocotrienol: in vivo and in vitro Studies

Ko et al[62] explored the effects of dietary vitamin E supplementation in Wistar rats, focusing on serum vitamin E levels, RGC density, and oxidative stress markers. The findings indicated that rats receiving a vitamin E-enriched diet exhibited significantly higher serum tocopherol levels compared to the standard diet group. However, despite this elevation, RGC density remained statistically unchanged between the standard and supplemented groups. Notably, the vitamin E-deficient group exhibited a significant reduction in RGC counts, emphasizing the importance of adequate vitamin E intake in maintaining retinal integrity.

Furthermore, oxidative stress markers, including SOD, GSH, and catalase, showed no significant alterations in the standard and deficient diet groups following IOP elevations. However, lipid peroxidation levels were markedly higher in the deficient group, reinforcing the hypothesis that vitamin E plays a protective role against oxidative stress in ocular tissues.

The study by Tanito et al[63] provided a complementary perspective, investigating the intraocular penetration of tocopherols and tocotrienols when administered via topical and oral routes. Interestingly, their findings revealed that topical application of α-tocotrienol (α-Toc-3) led to a more pronounced increase in ocular tissue concentrations compared to α-tocopherol (α-Toc). Similarly, γ-tocotrienol (γ-Toc-3) exhibited a significantly greater intraocular accumulation when administered topically rather than orally. This suggests that tocotrienols, particularly in topical formulations, may serve as a superior delivery mechanism for ocular bioavailability, a crucial factor for therapeutic applications.

The study by Rego et al[61] provides crucial insights into the dual role of vitamin E succinate in retinal cells derived from chick embryos. At low concentrations (10–20 mM), vitamin E succinate was found to enhance plasma membrane integrity by reducing lactate dehydrogenase (LDH) release. This suggests that moderate supplementation may confer protective effects against cellular damage, possibly by stabilizing membrane phospholipids and mitigating oxidative stress.

However, at higher concentrations (80 mM), vitamin E succinate exhibited cytotoxic properties, leading to increased LDH release and mitochondrial dysfunction. This was evidenced by decreased mitochondrial activity (only 36% of control levels in the MTT assay) and a dose-dependent reduction in the ATP: ADP ratio. Such findings highlight the importance of dosage optimization when considering vitamin E supplementation in therapeutic applications. Furthermore, vitamin E succinate demonstrated superior intracellular uptake and oxidative stress mitigation (reduced TBARS levels) compared to vitamin E acetate, indicating that specific vitamin E derivatives may exhibit varying degrees of bioactivity.

The study conducted by He et al[64] explored the effects of vitamin E on TM cells, which are crucial in regulating intraocular pressure (IOP) and are often compromised in primary open-angle glaucoma (POAG). The findings demonstrate that vitamin E at a concentration of 200 μM effectively reduced endogenous reactive oxygen species (ROS) levels in glaucomatous TM (GTM) cells ($p<0.05$). Furthermore, pretreatment with vitamin E significantly attenuated ROT-induced ROS production in GTM cells, although no significant effect was observed in normal TM (NTM) cells. This suggests that vitamin E selectively benefits diseased or stressed cells rather than exerting a blanket effect on all TM cell populations.

While the current evidence highlights the antioxidant and neuroprotective potential of tocopherol and tocotrienol in glaucoma management, it is essential to acknowledge that the overall findings remain heterogeneous and occasionally inconsistent. Several large-scale cohort and Mendelian randomization studies[30,37,40,41] reported no significant association between dietary or serum vitamin E levels and glaucoma risk or progression. These findings suggest that the observed benefits of vitamin E derivatives in experimental settings may not consistently translate into measurable clinical outcomes. Furthermore, differences in dosage, formulation, bioavailability, and study design contribute to variability in the reported effects. Therefore, although preclinical studies consistently demonstrate the neuroprotective and IOP-lowering potential of vitamin E isoforms, clinical evidence remains limited and inconclusive. Future investigations should aim to bridge this translational gap through well-controlled, longitudinal trials that compare tocopherol and tocotrienol efficacy while considering confounding factors such as age, diet, and comorbidities. A balanced interpretation of both positive and null findings is crucial to avoid overstating clinical benefit and to guide realistic therapeutic expectations for vitamin E in glaucoma management.

Challenges and Limitations in Managing Glaucoma

Tocotrienol and Tocopherol: Bioavailability and Synergy

Tocopherol and tocotrienol, two primary isoforms of vitamin E, have shown significant potential in addressing the pathophysiological mechanisms underlying glaucoma, a progressive optic neuropathy that leads to irreversible blindness. However, their therapeutic application is hindered by challenges in drug delivery, particularly in achieving effective bioavailability and targeted delivery to ocular tissues. Drug delivery systems face significant obstacles in navigating the complex anatomy and

physiology of the eye, including barriers like the tear film, cornea, and blood-retinal barrier.[65] It is due to the human eye being an intricate organ, featuring millions of cones, rods and ganglion cells.[66] Topical administration, the most common route for glaucoma treatment, is limited by low bioavailability, as only a small fraction of the administered dose reaches the intraocular tissues.[67] Despite this limitation, it remains the primary therapy for glaucoma due to its ability to deliver drugs directly to the targeted site, ensuring greater localization and minimal systemic absorption compared to oral supplementation.

Among the vitamin E isoforms, tocopherol, particularly α-tocopherol, is better suited in our ocular due to its structural properties. It is assumed that its saturated isoprenoid side chain allows strong binding to tear lipocalin (TL), a hydrophobic molecule transporter in the tear film. This interaction enhances its stability and facilitates penetration through the cornea, making it more effective in protecting and stabilizing the tear film against oxidative damage.[68,69] Tocopherol is relatively higher bioavailability in ocular tissues, combined with its antioxidant activity, supports its role as a promising therapeutic candidate for glaucoma management.

In contrast, tocotrienol faces greater delivery challenges due to its possibility of the unsaturated side chain, which reduces its compatibility with TL and weakens its corneal penetration capabilities. The hydrophobic nature of tocotrienol limits its solubility in the tear film, further restricting its ability to reach the posterior segment of the eye where neurodegeneration occurs.[70] Systemically, previous study showed that tocotrienol is also disadvantaged by lower oral bioavailability,[71] rapid clearance with a half-life of 2.3 to 4.4 hours, and dependence on specific transport proteins for absorption.[72,73] Study by Mohamad,[74] proposed that tocotrienol requires synergy with α-tocopherol, as well as optimal fat levels and suitable conditions, to achieve its full therapeutic potential.

Moreover, study showed that the formulation of microemulsion and liposomal tocotrienol has demonstrated an anticataract effect, which can be attributed to reduced lenticular oxidative stress and attenuation of nitrosative stress.[70] Most of the treatments associated with tocotrienol has been combined with other compounds. Despite these limitations, tocotrienol exhibits stronger antioxidant activity than tocopherol,[75] which could be leveraged with advanced drug delivery systems to overcome its bioavailability issues.

Current Advancements in Novel Vitamin-E-Based Drug Delivery System in Managing Glaucoma

Traditional treatment methods, including eye drops and oral medications, have limitations such as poor bioavailability, limited efficacy, and poor patient adherence. However, various innovative interventions aimed at enhancing drug delivery, targeting affected tissues more efficiently.

Contact Lens

Contact lenses have emerged as an innovative ocular drug delivery system, significantly improving drug bioavailability compared to traditional eye drops. Designed to fit the cornea, contact lenses are made from hydrophilic or hydrophobic polymers, with soft contact lenses composed of hydrogel or silicone hydrogel being more popular due to their biocompatibility, comfort, and hydrophilic properties.[76] Unlike eye drops, which have low bioavailability (1%–5%) and require multiple daily instillations leading to poor patient compliance, contact lenses provide prolonged and controlled drug release directly to the cornea, achieving bioavailability exceeding 50% under ideal conditions.[77]

A study found that over 60% of patients preferred contact lenses for glaucoma treatment due to reduced drug administration frequency, particularly those aged 30–49.[78] Moreover, while improper instillation of eye drops is common and can cause suboptimal treatment or side effects, contact lenses eliminate these challenges, offering better drug absorption and improved therapeutic outcomes.[79] The physical properties of drug-releasing contact lenses, including transparency, oxygen permeability, and water content, are critical in ensuring effective drug loading, sustained release, and user safety, making them a superior alternative to conventional eye drop therapies.[76]

Nanotechnology

Current advancements in glaucoma eye drop delivery include nanoliposomes and nanoparticles (Figure 7), which aims to enhance drug retention and controlled release.

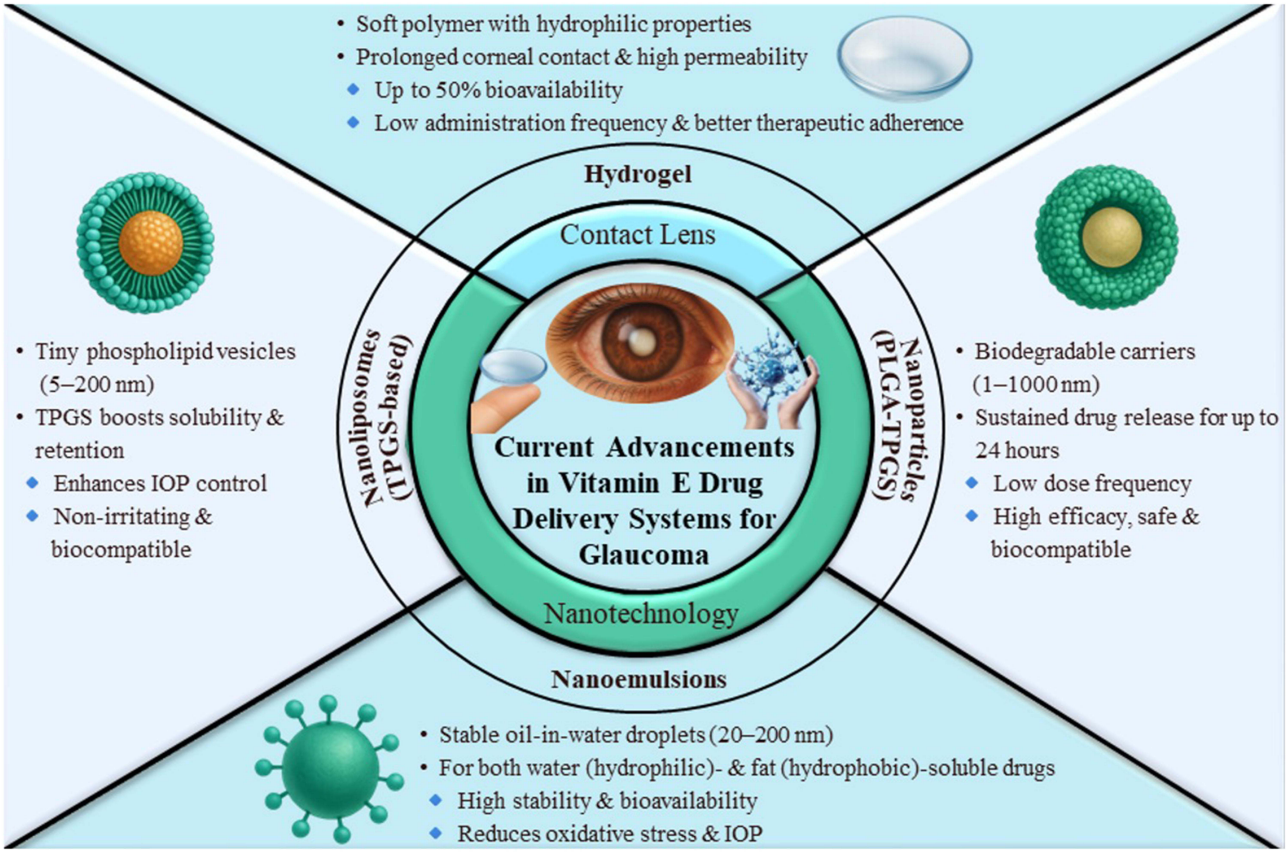

Figure 7 Current advancements in vitamin E drug delivery systems for glaucoma.[26,45,46,77,80–83]
Note: Figure created using Canva.

Nanoliposomes (TPGS)

Nanoliposomes, the first nano-drug delivery system approved by the United States Food and Drug Administration (FDA) in 1995, are versatile nanocarriers capable of solubilizing hydrophobic drugs by embedding them in their lipid bilayer.[80,84] Novel liposomes for eye drop improve corneal permeability through close contact with ocular tissues and prolonged retention time on the cornea.[85–87]

Nanoemulsion

Nanoemulsions (NE), heterogeneous dispersions with droplet sizes of 20–200 nm,[81] provide an effective platform for solubilizing both hydrophilic and hydrophobic drugs, improving the eye drop bioavailability, and protect from enzymatic degradation. Their high stability against flocculation and phase separation ensures a long shelf life.[88] α-Tocopherol with the combination of latanoprost in NE have demonstrated the ability to prevent fundus cell apoptosis, clear reactive oxygen species (ROS) in the fundus, and reduce IOP both in vitro and in vivo study.[82] Their biodegradable and biocompatible nature further supports their use in glaucoma therapy, making them a promising intervention.

Nanoparticles (PLGA-TPGS)

Nanoparticles, submicron-sized carriers typically ranging from 1–1000 nm, represent a promising advancement in ocular drug delivery due to their ability to encapsulate hydrophilic drugs within a lipophilic matrix.[80] This approach enhances ocular drug retention, transcorneal transport, and intraocular bioavailability. A study employing PLGA, a biodegradable, biocompatible, and FDA-approved polymer, combined with vitamin E TPGS as an emulsifier, demonstrated the potential of nanoparticles for topical glaucoma therapy. TPGS, being 77 times more effective than traditional PVA as an emulsifier, ensures superior drug encapsulation and acts as a P-glycoprotein inhibitor to enhance drug delivery.[44,45,88,89]

Furthermore, the incorporation of PLGA-TPGS nanoparticles into a thermosensitive in situ gel matrix improves precorneal residence time, prevents rapid drainage, and enables sustained drug release for up to 24 hours without causing ocular irritation in glaucoma-induced white New Zealand rabbits.[46]

A Paradigm Shift from Tocopherol to Tocotrienol in Glaucoma Management

Tocopherols have long been recognized for their antioxidant properties, primarily sourced from soybeans, olive oil, and leafy greens.[90] However, recent research trends indicate a growing interest in tocotrienols as a superior alternative, particularly in managing neurodegenerative diseases like glaucoma. According to Ranasinghe et al[19] and Szewczyk et al[91] the increasing focus on tocotrienols stems from their distinct biochemical properties and potential therapeutic benefits, unlike tocopherols, tocotrienols exhibit stronger antioxidant capabilities, enhanced anti-inflammatory effects, and superior neuroprotective mechanisms. These unique attributes make them particularly attractive for addressing the oxidative stress and neurodegeneration associated with glaucoma.[92] Tocotrienols have emerged as a promising candidate due to their ability to modulate cellular pathways implicated in retinal health and vision preservation.[20]

Emerging hypotheses suggest that tocotrienols may be more effective in glaucoma management due to their enhanced ability to penetrate lipid membranes and modulate key pathways implicated in oxidative stress and neurodegeneration.[20] Comparative studies indicate that tocotrienols exhibit stronger inhibition of retinal ganglion cell apoptosis, making them a promising alternative to conventional Vitamin E forms.[12,93] Although tocotrienols have a shorter half-life and lower bioavailability than tocopherols, these characteristics may contribute to their targeted efficacy in ocular tissues, reducing oxidative damage and apoptosis of retinal ganglion cells.[94] In line with that, Tocotrienols have been reported to regulate lipid metabolism and inflammatory pathways more effectively than tocopherols, further reinforcing their potential therapeutic benefits.[19]

Despite tocotrienols' promising potential, tocopherols remain the most extensively studied Vitamin E compounds.[95] However, as the understanding of glaucoma advances, the unique attributes of tocotrienols warrant further investigation, positioning them as a compelling candidate for future therapeutic applications.[12] With increasing evidence supporting their benefits, tocotrienols could pave the way for new and improved treatments for glaucoma, offering hope to millions affected by this debilitating condition.[18] As scientific exploration continues, tocotrienols may ultimately redefine the role of Vitamin E in neurodegenerative disease management, solidifying their place in ophthalmic and neurological research.

Conclusion and Future Directions

Despite encouraging preclinical and limited clinical evidence supporting the neuroprotective role of vitamin E isoforms, the current body of research remains insufficient to justify its recommendation as a therapeutic option for glaucoma. Considerable challenges persist in improving vitamin E ocular bioavailability, stability, and targeted delivery to the posterior segment of the eye. A more definitive understanding of its therapeutic efficacy will require well designed, adequately powered randomized controlled trials that can validate the translational potential observed in laboratory and early clinical studies. Such trials should also consider pharmacokinetic variability, optimal dosage forms, and potential interactions with current glaucoma medications. Tocopherol continues to hold clinical promise due to its established antioxidant profile and safety, while tocotrienol offers additional mechanistic advantages that merit further exploration. Future studies investigating the synergistic combination of tocopherol and tocotrienol with other neuroprotective agents, including omega-3 fatty acids, polyphenols, or existing intraocular pressure-lowering drugs, may open new avenues for multimodal glaucoma therapy. With the advancement in nanotechnology-based delivery systems, such as biodegradable nanoparticles, nanoemulsions, and sustained-release ocular inserts, present an exciting opportunity to enhance the localized delivery and therapeutic efficacy of vitamin E compounds. Collectively, by addressing these gaps and pursuing more rigorous clinical validation, vitamin E derivatives may eventually emerge as valuable adjunctive agents in glaucoma management, contributing to improved neuroprotection, visual preservation, and overall patient outcomes.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author(s) used ChatGPT 4.0 to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this publication.

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