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# The use of vitamin E in ocular health: Bridging omics approaches with Tocopherol and Tocotrienol in the management of glaucoma

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ABSTRACT

Vitamin E, encompassing tocopherols and tocotrienols is celebrated for its powerful antioxidant properties, which help neutralize free radicals and protect cells from oxidative damage. Over the years, research has shown that both tocopherols and tocotrienols offer significant benefits, including protection against radiation damage, cholesterol regulation, cardiovascular health, and neurological disorders. This wide range of benefits highlights the need for further exploration of vitamin E's role in managing various diseases. One particularly promising area is its potential application in treating ocular diseases like glaucoma. Despite advances in treatment, current options have limitations, making the investigation of alternative approaches crucial. Omics technologies, which allow for a detailed examination of biological systems, could provide valuable insights into how tocopherols and tocotrienols work at a molecular level. Their neuroprotective and antioxidative properties make them promising candidates for glaucoma management. Additionally, the sustainability of vitamin E is noteworthy, as by-products from its production can be repurposed into valuable resources for nutraceuticals and pharmaceuticals. As research continues, integrating omics technologies with the study of vitamin E derivatives could unveil new therapeutic possibilities, further enhancing our understanding of its diverse health benefits and its potential role in preventing and managing diseases.

## 1. Introduction

Vitamin E is an integral component of the human diet and is synthesized solely by autotrophic organisms. Sources of vitamin E are abundantly present in nature, including green leafy vegetables, nuts, seeds, and plant oils. Tocopherols, the primary forms of vitamin E, exhibit a distinct distribution pattern within the plant kingdom: α-tocopherol predominates in green leafy plants, while γ-tocopherol is prevalent in non-green plant parts such as fruits and seeds (U.S. Department of Agriculture, Agricultural Research Service, 2019). Common foods that serve as sources of α-tocopherol include almonds, avocados, hazelnuts, peanuts, and sunflower seeds. β-tocopherol can be found in oregano and poppy seeds, while γ-tocopherol is abundant in pecans, pistachios, sesame seeds, and walnuts (U.S. Department of Agriculture, Agricultural Research Service, 2019). Edamame and raspberries are notable sources of δ-tocopherol. In contrast, an intriguing hypothesis suggests that tocotrienols may undergo bioconversion into tocopherols, potentially serving as intermediates in the biosynthesis of α-tocopherol within plants (Peh et al., 2016; Pennock, 1983; Szewczyk et al., 2021). This hypothesis unveils a dynamic interplay between these vitamin E variants, adding another layer of complexity to plant physiology. Tocotrienols are prominently present in the seed endosperm of most monocots, fruits of dicotyledonous plants, and the latex of rubber trees (Horvath et al., 2006; Zeng et al., 2024). Palm oil and crude oil are recognized for their high concentrations of tocotrienols, with levels reaching up to 800 mg/kg in weight, predominantly comprising α-tocotrienol and γ-tocotrienol isotypes (Sen et al., 2010).

## 2. The discovery of vitamin E

A century ago, a groundbreaking discovery at the University of California revealed the presence of vitamin E in green leafy vegetables, thanks to the pioneering work of Herbert Evans and Katherine Bishop (Evans & Bishop, 1922; Miyazawa et al., 2019). The compound, scientifically named Tocopherol from the Greek word for "to bear offspring," was chemically synthesized in 1983 (Miyazawa et al., 2019; Sen et al., 2007). In 1964, Tocotrienol was identified by Pennock and Whittle, isolated from rubber (Dunphy et al., 1965; Aggarwal et al., 2010;

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Miyazawa et al., 2019). The terminology for vitamin E encompasses both Tocopherol and Tocotrienols, which are characterized by their two rings and hydrocarbon chains.

Natural vitamin E exists in several forms: α, β, γ, and δ, differing based on the methyl or proton groups attached to their benzene rings (Mohd Zaffarin et al., 2020). Synthetically, it is produced from eight stereoisomers, with RRR-α-tocopherol being the most pharmacologically active form. Tocopherols have a saturated aliphatic phytyl side chain, while tocotrienols possess an unsaturated farnesyl side chain with three double bonds, as illustrated in Fig. 1. The differences in their side chains influence their behavior in the human body. Tocopherols integrate stably into cell membranes, offering effective antioxidant protection by neutralizing free radicals and preventing oxidative damage to lipids, proteins, and DNA (Mesa & Munné-Bosch, 2023).

In contrast to tocopherols, tocotrienols, with their unsaturated side chains, penetrate and move within lipid bilayers more easily (Sen et al., 2007; Ahsan et al., 2014; Mohd Zaffarin et al., 2020). This structural characteristic allows tocotrienols to reach and act within tissues more effectively than tocopherols, providing superior antioxidant capabilities and enhanced protection against oxidative stress. This stress is implicated in the development of various chronic diseases, including cardiovascular diseases and cancer (Sen et al., 2007; Shrum et al., 2023; Talib et al., 2024). The difference in side chain structure contributes to tocotrienols' greater affinity for lipid membranes compared to tocopherols (Mohd Zaffarin et al., 2020), leading to higher bioavailability in tissues. Moreover, vitamin E, which is present in cell membranes and lipoproteins, plays a role in the peroxidation of cell membrane lipids (Miyazawa et al., 2019; Villalón-García et al., 2022; Sezer et al., 2020). Tocopherols, especially α-tocopherol, are efficiently released from the liver into the bloodstream by α-tocopherol transfer protein (α-TTP), allowing their accumulation in various organs. In contrast, tocotrienols have a lower affinity for α-TTP and are less likely to enter the bloodstream from the liver (Miyazawa et al., 2019). Instead, tocotrienols may accumulate in the brain and adipose tissue via the lymphatic system (Miyazawa et al., 2019; Peh et al., 2016). As vitamin E isoforms vary in bioavailability and metabolic processes, only α-tocopherol is selectively retained in plasma and tissues through the action of hepatic α-TTP, saturating them at approximately 90 %. Other isoforms of vitamin E are degraded and excreted (Jiang, 2017; Lee & Ulatowski, 2019; Szewczyk, Chojnacka, & Górnicka, 2021; Traber et al., 2010). Vitamin E is a potent antioxidant that effectively neutralizes free radicals by scavenging lost electrons, thereby protecting cells from oxidative damage and contributing to overall health (Institute of Medicine Panel on Dietary & Related, 2000; Szewczyk et al., 2021). Fig. 2 illustrates the growing interest in vitamin E over the years.

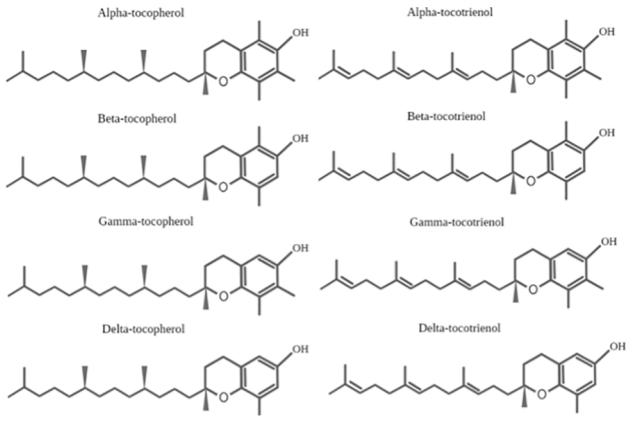


**Fig. 1.** The phytochemistry of Tocopherol and Tocotrienol. Retrieved from Chin & Ima-Nirwana (2012) and recreated using Biorender.com.

## 3. Sustainability use of vitamin E

The concept of converting waste materials into valuable resources, commonly termed "upcycling" or "valorization," entails the innovative repurposing or extraction of value from materials otherwise destined for disposal (Bejenaru et al., 2024). In the case of waste Tocopherol and Tocotrienol, which are forms of vitamin E often derived from sources like vegetable oils and green leafy vegetables, residual products derived from diverse industrial processes possess latent potential for multifaceted applications beyond their primary utilization (Gupta et al., 2019). Before the industrial era, the oil palm tree Elaeis guineensis, native to West and Central Africa, is known for its high yield of palmitic acid and has a significant vitamin E content (Kiple & Ornelas, 2000; Sen et al., 2010; Ian, 2012; Haran et al., 2020; Loganathan et al., 2020). In the 15th century, indigenous communities in these regions extensively utilised the oil palm tree for various purposes (Ian, 2012). Palm oil was a staple in local diets, used for cooking as it has potent antioxidants that support the consistency of the oil during cooking and as a flavouring agent (Wattanapenpaiboon & Wahlqvist, 2003). Additionally, the oil palm tree was integral to traditional medicine as skin ointment and a common antidote to poisons (Ekwenye & Ijeomah, 2005; Owoyele, 2014). Recognizing the diverse applications and significant importance of palm oil in daily life, cultivation of the oil palm was expanded in the 19th century. The oil palm was introduced to Southeast Asia for commercial purposes, primarily to produce soap which has been used for skin infections, margarine, and cooking oil for export (Ian, 2012; Sundram et al., 2003). Employing pioneering methodologies spanning nutraceuticals, pharmaceuticals, functional foods, animal feed additives, biofuel production, and industrial applications, these compounds can be reimagined as high-value commodities (Mohamad, 2023; Szewczyk et al., 2021), not only capitalise on underutilised resources but also align with broader sustainability objectives by curtailing waste generation and optimizing resource utilization. The transformation of waste Tocopherol and Tocotrienol into coveted assets not only addresses environmental imperatives but also engenders novel economic opportunities across diverse sectors, thereby fostering a circular and sustainable economic paradigm (Ogawa & Iuchi, 2024).

## 4. Potential role of Tocopherol and Tocotrienol

The historical trajectory of Tocopherol and Tocotrienol research traces its roots to the early 1920s, playing a vital role in human health. The exploration of this compound dates back to the early 20th century when researchers began to recognize the importance of specific dietary factors in preventing deficiency diseases. Insufficient levels of this vitamin are now acknowledged as a prominent factor in the onset of severe degenerative conditions, such as ataxia, muscle degeneration, Duchenne muscular dystrophy, and infertility (Aggarwal et al., 2010; Kemnic & Coleman, 2023). Filer and Mason were the first researchers to demonstrate the vital role of vitamin E in protecting unsaturated fatty acids from in vivo oxidation, while also conducting studies on the repercussions of vitamin E deficiency in rhesus monkeys. This research marked the initial exploration of such deficiency studies in any primate species, including humans (Bell, 1987; Dinning & Day, 1957; Filer et al., 1949; Mason & Telford, 1947). Each year brings forth a multitude of novel therapies developed using the unique properties of vitamin E, making it a promising agent in addressing diverse diseases, as shown in Fig. 3.

Tocopherols, particularly d-α-Tocopherol (RRR-α-Tocopherol), characterized by their chromanol ring and phytyl tail, have long been recognized for their high bioavailability and established antioxidant properties, making them a cornerstone of vitamin E research (Kuchan et al., 2018; Traber & Atkinson, 2007). In contrast, Tocotrienols, although historically overshadowed in vitamin E research, offer distinct biological activities that have garnered increasing attention. Structurally, Tocotrienols differ from Tocopherols by possessing an isoprenoid

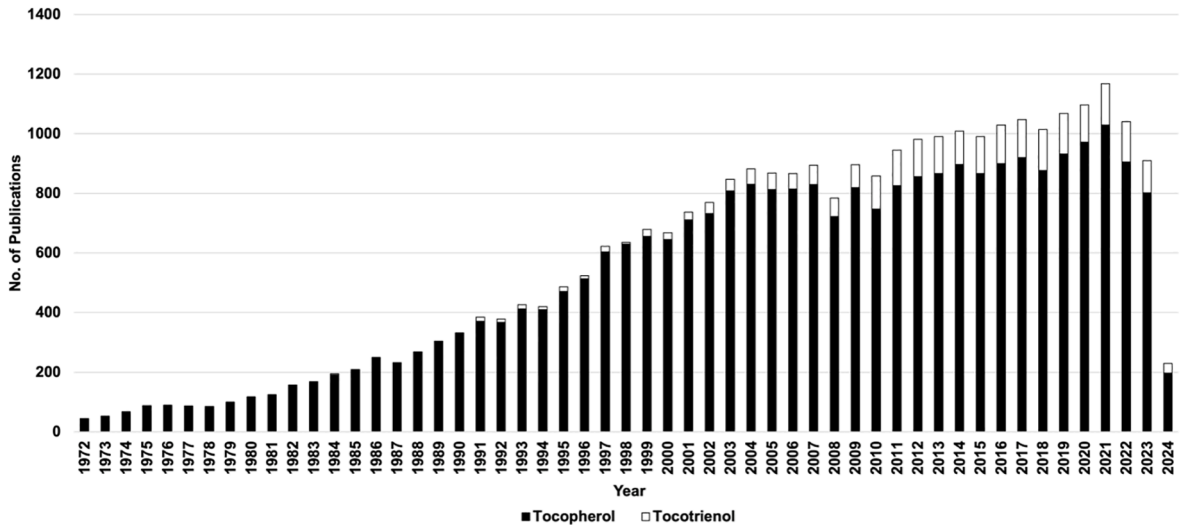


**Fig. 2.** The interest in vitamin E research was published in PubMed from 1972 to 2024.

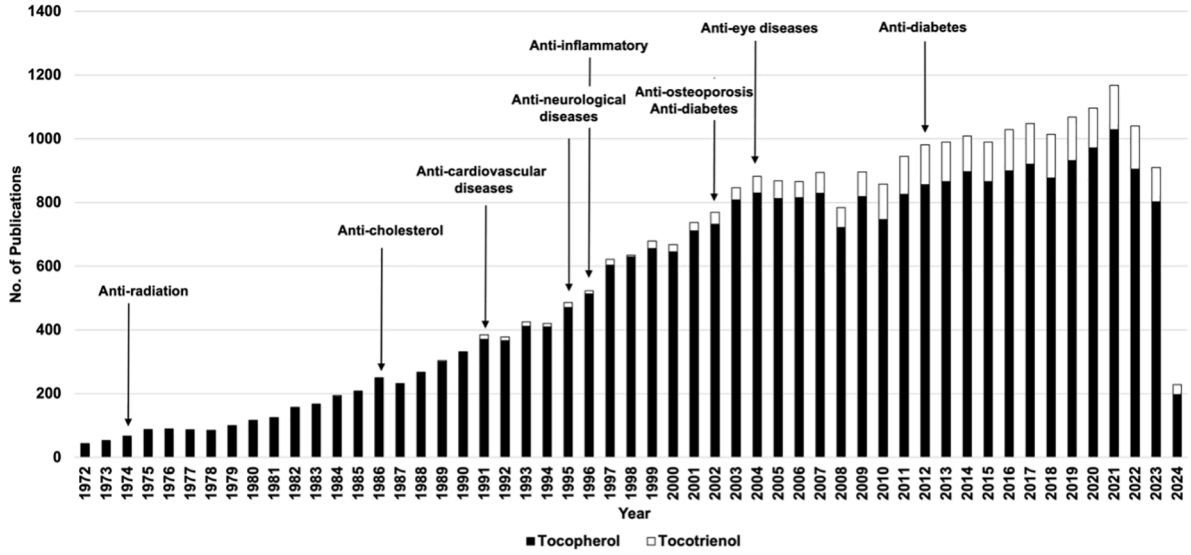


**Fig. 3.** The discovery potential of vitamin E.

tail with three unsaturation points, which imparts unique functional properties to these compounds (Miyazawa et al., 2019; Ranasinghe et al., 2022; Sen, Khanna, & Roy, 2006). This structural variation confers upon Tocotrienols potent neuroprotective, antioxidant, anti-cancer, and cholesterol-lowering effects, which have been demonstrated in numerous preclinical and clinical studies (Sen, Khanna, & Roy, 2006, 2007; Shrum et al., 2023; Talib et al., 2024). Despite their lower oral bioavailability compared to Tocopherols, Tocotrienols have shown promising efficacy in protecting neurons against neurotoxic insults and modulating various signaling pathways implicated in disease pathogenesis (Ranasinghe, Mathai, & Zulli, 2022; Sen, Khanna, & Roy, 2007). These insights underscore the importance of evaluating the roles of Tocopherols and Tocotrienols in health and disease and exploring their distinct contributions to human physiology (Table 1), paving the way for novel therapeutic interventions and personalized approaches to healthcare (Sen, Khanna, & Roy, 2007).

## 5. Bridging current interest with a future therapeutic target in glaucoma

Around 1525 BCE, delving into the intriguing historical landscape of Ancient Egypt reveals a substantial focus on ocular health, particularly in the Ebers Papyrus (Andersen, 1997). Human eyes are a masterpiece of complexity, consisting of three million cones (responsible for transmitting color), one hundred million rods (sensitive to low-light conditions), and 1.5 million ganglion cells (Sánchez López de Nava et al., 2023). Human vision can be susceptible to various diseases due to genetic, environmental, and lifestyle factors. Ocular diseases encompass a broad spectrum of disorders affecting various components of the eye, ranging from the cornea to the retina. Approximately 80 % of individuals experiencing blindness reside in developing nations, primarily in rural regions where access to eye-care facilities is limited or underutilized (Wang et al., 2013). Glaucoma, a prevalent ocular disorder characterized by elevated intraocular pressure (IOP) and subsequent optic nerve damage, poses a substantial global health concern. Despite advancements in treatment, current glaucoma therapies encounter significant limitations, including undesirable side effects and inadequate efficacy (Davis et al., 2016; Garcia-Medina et al., 2020; Marcus et al., 2019). Building on the wealth of Vitamin E research, which includes 47, 691 publications since 1927, Tocopherol and Tocotrienol are being explored as alternatives for treating glaucoma by reducing intraocular pressure. Recognizing the extensive knowledge amassed in the field, the

**Table 1**
The role of Tocopherol and Tocotrienol in a spectrum of diseases.

| Therapies | Role | Reference |
|---|---|---|
| Anti-radiation | ● α-Tocopherol preserves the hematopoietic system, crucial for averting radiation-induced cytopenia and aiding blood cell recovery. It serves as a chain-breaking antioxidant, halting the lipid peroxidation reactions.<br>● δ-Tocotrienol shields mouse bone marrow and human CD34+ cells from radiation damage through Erk activation, emphasizing its protective role via mTOR survival pathways. | (Felemovicius et al., 1995; Li et al., 2010; Ranasinghe et al., 2022; Satyamitra et al., 2011; Sovira et al., 2020) |
| Anti-cholesterol | ● Vitamin E entirely prevents cholesterol-induced atherosclerotic lesions and the expression of CD36 mRNA.<br>● Tocotrienols reduce serum cholesterol levels and inhibit enzymes in the cholesterol biosynthetic pathway, including, 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase and cholesterol 7 α-hydorxylase. | (Catalgol & Ozer, 2012; Qureshi & Qureshi et al., 1991; Xiong et al., 2023) |
| Anti-cardiovascular disease | ● α-Tocopherol reduces lipid peroxidation, monocyte proatherogenicity, and platelet aggregation.<br>● γ-Tocopherol eliminates peroxynitrite-derived reactive nitrogen species (RNS).<br>● Tocotrienol stabilizes proteasomes, ensuring the balance of survival and apoptotic signals, promoting myocardial health. | (Das et al., 2008; Devaraj & Jialal, 1998; Kaul et al., 2001; McCarty, 2007; Pei et al., 2015; Qureshi et al., 2011; Ramanathan et al., 2018; Sovira et al., 2020) |
| Anti-neurological diseases | ● α-Tocotrienol and γ-Tocotrienol enhance tyrosine hydroxylase (TH) expression, dopamine (DA) neurons, and striatal fibers in 6-OHDA-induced rats. | (Kumari et al., 2021) |
| Anti-inflammatory | ● α-tocopherol lowered the inflammatory level as observed by reduced macrophage infiltration and JNK/c-Jun signalling.<br>● γ-Tocopherol efficiently traps inflammation-induced electrophiles, detoxifying nitrogen dioxide ($NO_2$) and peroxynitrite to form 5-nitro-γ-tocopherol. | (Christen et al., 1997; Demirel-Yalciner et al., 2021) |
| Anti-osteoporosis | ● Vitamin E scavenges and neutralizes free radicals, preventing their activation of the NFκB transcription factor. It lowers bone-resorbing cytokine levels and inhibits NFκB activation by boosting internal antioxidative enzymes in the bone. | (Ahmad et al., 2005; Nazrun et al., 2012; Wong et al., 2019) |
| Anti-diabetes | ● Tocopherols enhance the retinal blood flow and alleviates renal dysfunction in type 1 diabetes, without changing the glycated haemoglobin levels.<br>● Tocotrienol-rich fraction improves blood glucose, lipids, and oxidative stress in streptozotocin-induced diabetic rats, preserving aortas, reducing glycosylation end products, and enhancing glycemic control.<br>● Beta-tocotrienol intake significantly associates with a reduced risk of type 2 diabetes mellitus. | (Budin et al., 2009; Bursell et al., 1999; Chin et al., 2011; Montonen et al., 2004; Pang & Chin, 2019; Wan Nazaimoon & Khalid, 2002) |
| Anti-eye diseases | ● Tocopherols intercept lipoperoxidation product formation by scavenging free radicals and shielding the retina from oxidative injury.<br>● Tocotrienol reduces oxidative and nitrosative stress in catarctogenesis formation. | (Abdul Nasir et al., 2014; Edwards et al., 2022; Shrum et al., 2023; Zapata et al., 2008) |
| Anti-asthma | ● α-tocopherol (antagonist of PKCα activity) and γ-tocopherol (agonist of PKCα activity) directly bind to the C1a regulatory domain of PKCα. Thus, regulating leukocyte modulating during allergic inflammation. | (Cook-Mills & Avila, 2014; McCarty, 2007) |

focus is now on these vitamin E constituents to provide a novel perspective on glaucoma management. Table 2 summarizes studies that highlight the potential roles of Tocopherol and Tocotrienol as therapeutic agents in ocular diseases.

## 6. Integrating omics approaches in understanding the antioxidative properties of vitamin E

Tocotrienols and tocopherols are well-established for their antioxidative properties. The use of omics technologies, such as genomics, proteomics, metabolomics, and transcriptomics, offers powerful tools for comprehensively studying biological systems. These technologies can analyze the molecular components of food waste and by-products, revealing valuable insights into their composition and potential applications. When combined with the exploration of Vitamin E derivatives, omics technologies present exciting opportunities for addressing unmet needs in glaucoma management. The antioxidant activity of vitamin E is mediated by the phenolic hydroxyl group, which quickly donates hydrogen to peroxyl radicals, leading to the formation of a stable lipid species (Lü et al., 2010). Vitamin E itself becomes a relatively unreactive free radical, as the unpaired electron is delocalized into the aromatic ring. The efficiency of this protection is regulated by two factors: first, the molecule's mobility in membranes, determined by its aliphatic tail; and second, the number of methyl groups on the chromanol ring, with each methyl group enhancing antioxidant activity (Celik et al., 2013; Fujisawa & Kadoma, 2005; Phaniendra et al., 2015; Rimbach et al., 2010).

In this context, vitamin E can scavenge peroxyl radicals, effectively neutralizing them to generate hydroperoxides. Lipid peroxyl radicals are produced during lipid peroxidation. Following an initiating event, such as a reactive oxygen species, a hydrogen molecule is extracted from a

**Table 2**
Studies Related to Tocopherol and Tocotrienol in Ocular Diseases.

| | Disease | Findings | References |
|---|---|---|---|
| Tocopherol | Glaucoma | ● In addition, tocopherols function as neuroprotective agents, vasoregulators, endothelial cell survival time extender in rabbits, and shield the cell membranes of photoreceptor cells.<br>● Alpha-tocopherols also modifies retinal vascular dysfunction resulting from hyperglycemia. | (Chaudhry et al., 2022) |
| | Cataract | ● Lipid oxidation levels were low in the vitamin E group and high in the GSH and GPx antioxidant.<br>● Chick embryos are protected against glucocorticoid-induced cataract development by the potent antioxidant vitamin E. | (Vurmaz et al., 2021) |
| | Diabetic retinopathy | ● Reduce reactive oxidative stress and inhibit angiogenesis.<br>● Diabetic retinopathy is linked to increased levels of reactive oxygen species such as the overproduction of superoxide radical anion, hydroxyl radical, hydrogen peroxide ($H_2O_2$), and singlet oxygen.<br>● Mean serum vitamin E levels that were significantly lower in diabetic retinopathy than those of those without. | (Ruamviboonsuk and Grzybowski, 2022; Sies and Jones, 2020; Gao et al., 2023) |
| Tocotrienol | Cataract | ● Reduce the cataract's onset and progression.<br>● It was suggested that reducing lenticular nitrosative and oxidative stress might prevent cataracts by decreasing lens aldose reductase activity, oxidative-nitrosative stress, and NF-κB activation, which would lower iNOS expression and calpain activity. | (Sharma et al., 2022) |
| | Diabetic Retinopathy | ● Reduced the retinal NFκB activation, IL-1β, IL-6, TNF-α, IFN-γ, iNOS, and MCP-reduced retinal expression of VEGF, IGF-1, and HIF-1α lowers retinal cell death, and conserved the retinal layer thickness and retinal venous diameter. | (Sadikan et al., 2022; Sadikan et al., 2023) |

C—H bond that has been weakened by its proximity to an electron-withdrawing double bond found in polyunsaturated fatty acids, resulting in the formation of a carbon-centered radical (Niki, 2014; Valgimigli, 2023). During this process, the lipid undergoes molecular rearrangement to a conjugated diene structure, and $O_2$ is added to the carbon-centered radical, producing a lipid peroxyl radical (Ayala et al., 2014; Niki, 2014; Valgimigli, 2023). This radical is extremely reactive and, if not quenched, will combine with a neighboring polyunsaturated fatty acid, resulting in another initiating event and thereby propagating lipid peroxidation (Chaudhary et al., 2023; Endale et al., 2023; Nam, 2011). Vitamin E acts as a peroxyl radical scavenger, inhibiting this chain reaction, which is why it is referred to as a chain-breaking lipid antioxidant. Without vitamin E activity, a single initiating event may result in the formation of thousands of lipid peroxides, which would be detrimental to the biological membrane's function.

Vitamin E does not function alone; rather, it is part of a network of redox antioxidants. A recent study suggests that the properties of vitamin E's long-chain metabolites (LCMs) are similar to those of vitamins A and D (Bartolini et al., 2021; Kluge et al., 2021; Liao et al., 2022; Neukirch et al., 2021; Schubert et al., 2018). The molecular similarity between vitamin E metabolites and those of vitamins A and D (such as 9-*cis*-retinoic acid and 1,25(OH)2D3) suggests the existence of previously unknown vitamin E-specific receptors (Bartolini et al., 2021; Kluge et al., 2021; Liao et al., 2022; Neukirch et al., 2021; Schubert et al., 2018). This idea is supported by findings on the regulatory activities of vitamin E metabolites. In recent years, tocopherols and tocotrienols have gained popularity as evidence of their ability to prevent common ailments has emerged (Abraham et al., 2019; Azzi, 2017; Constantinou et al., 2020; Ramanathan et al., 2018; Shibata et al., 2016, 2017; Szewczyk et al., 2021; Tan et al., 2018; Uchida et al., 2018; Waniek et al., 2017; Wong et al., 2017; Wu et al., 2020).

Studies on anti-inflammatory effects often focus on the ability of vitamin E metabolites to regulate pro-inflammatory enzymes. Cyclooxygenase (COX), which catalyzes the synthesis of pro-inflammatory eicosanoids, plays a critical role in regulating the inflammatory response and contributes to the development of chronic diseases (Ricciotti & FitzGerald, 2011; Sheppe & Edelmann, 2021). α-Tocopherol metabolites (α-9′-COOH and α-13′-COOH) have been shown to decrease COX-1 and COX-2 activity, which produces pro-inflammatory eicosanoids (Jiang, 2014; Park et al., 2022). The α-tocopherol metabolite α-13′-COOH, in particular, acts as a competitive COX inhibitor and has a higher affinity for cyclooxygenases than other tocopherol forms (Pein et al., 2018). This metabolite also reduces inflammation by inhibiting 5-lipoxygenase (5-LO), which initiates the creation of immunomodulatory lipid mediators (Pein et al., 2018). It is proposed that vitamin E operates catalytically, efficiently reducing its free radical (chromanoxyl) form after quenching lipid radicals back to their native state (Rimbach et al., 2010). This catalysis occurs through interactions between water- and lipid-soluble molecules via both nonenzymatic and enzymatic pathways, which regenerate vitamin E from its tocotrienoxyl or tocopheroxyl radical back to tocotrienol and tocopherol, respectively. Vitamin C directly regenerates vitamin E, while thiol antioxidants like glutathione and lipoic acid renew vitamin E indirectly through vitamin C (Higgins et al., 2020; Ryan et al., 2010; Traber & Stevens, 2011). When these systems work together to maintain a low steady-state concentration of vitamin E radicals, vitamin E loss or consumption is minimized (Higgins et al., 2020; Ryan et al., 2010; Traber & Stevens, 2011).

## 7. Possible targets in management of glaucoma

Glaucoma comprises a collection of eye conditions that can damage the optic nerve, leading to vision impairment and, if not addressed, eventual blindness (Dietze et al., 2024). The primary characteristic of glaucoma is an elevation in intraocular pressure (IOP), which refers to the pressure within the eye (Raja et al., 2022). The root cause of this condition lies in the compromised drainage of aqueous humor, a clear

fluid produced by the eye to regulate IOP and nourish ocular structures (Praveen et al., 2022). In glaucoma, dysfunction in the drainage system, specifically the trabecular meshwork or Schlemm's canal, results in insufficient outflow of aqueous humor, leading to an increase in IOP (Sharif et al., 2023) and subsequent damage to the optic nerve.

Elevated IOP exerts mechanical stress on the optic nerve, jeopardizing its blood supply and damaging nerve fibers (McDowell et al., 2022). Since the optic nerve is responsible for transmitting visual information from the retina to the brain, any impairment to it can result in vision loss (Coleman-Belin et al., 2023). Fig. 4 visually represents the progression of glaucoma.

To date, our understanding of the specific pathways through which tocotrienols and tocopherols interact at the cellular level remains limited (Ranasinghe et al., 2022). However, according to Yang et al. (2020), both compounds share similar biochemical properties that influence their absorption and subsequent actions within the body. One crucial aspect of tocotrienols and tocopherols is their lipophilic nature, which facilitates their absorption in the digestive tract. Upon ingestion, these compounds are incorporated into mixed micelles in the small intestine, aiding in their solubilization and uptake into enterocytes (Górnaś et al., 2022). This process is predominantly mediated by passive diffusion, although certain transport proteins may also play a role in facilitating their absorption (Kiyose, 2021). The absorption processes are also mediated, at least in part, by three protein groups: Niemann-Pick C1-like 1 protein (NPC1L1), scavenger receptor class B type 1 (SRB1), and cluster of differentiation 36 (CD36) (Galmés et al., 2018; Jia et al., 2011; Kiyose, 2021; Yamanashi et al., 2017). These three proteins are primarily known as cholesterol transporters, but they can also bind to other substrates. Tocopherols and tocotrienols are absorbed in the intestine at rates ranging from 20 % to 80 % of the total amount ingested, which is lower than for other fat-soluble vitamins (Mohamad, 2023; Schmölz et al., 2016).

The simplified pathway for vitamin E transport and metabolism follows a pattern similar to that of other lipid species. Vitamin E is integrated into chylomicrons or HDL by intestinal epithelial cells using ABCA1 (Anwar et al., 2007; Hussain, 2014; Levy et al., 2021; Reboul, 2017) and transported to the liver or other tissues. In the liver, vitamin E is sorted and directed to catabolism or different lipoproteins before returning to the bloodstream. The transport route is the same for all forms of vitamin E. In the liver, α-TTP favors α-tocopherol over other forms, preventing excessive breakdown and excretion of the latter. The remaining forms of vitamin E are metabolized (phases I and II) (El Hadi et al., 2018; Traber, 2013). The uptake of different forms of vitamin E into the liver is most likely nonspecific.

Recent research has shown that supplementing with a combination of vitamin E isoforms leads to a significant increase in tocotrienol concentrations in tissues. This suggests that α-tocotrienol is transported differently within cells than α-TTP. Catignani and Bieri (1977) reported the first detection of α-TTP in rat liver. It is now generally acknowledged to be present in the brain, kidney, lung, spleen, uterus, and placenta, in addition to the liver (Hosomi et al., 1998; Copp et al., 1999; Kaempf-Rotzoll et al., 2002, 2003; Yamaoka et al., 2008; Rotzoll et al., 2008; Tamura et al., 2020; Edwards et al., 2022). The cytosolic 46-kDa α-tocopherol-associated protein (α-TAP) regulates the intracellular distribution of vitamin E (Stocker et al., 1999; Zimmer et al., 2000). It binds to α-tocopherol through chylomicron formation and lipids in the liver and acts as a metabolizing enzyme, increasing the uptake and absorption of vitamin E. This promotes anti-proliferative effects, particularly in prostate cancer, and acts as a tumor suppressor. The retina is expected to include α-TTP and α-TAP as it is a neuronal tissue with circuits that are an extension of the brain and nervous system (London et al., 2013; De Groef & Cordeiro, 2018).

Upon reaching their target sites, tocopherols and tocotrienols exhibit their antioxidative properties through various molecular pathways. One of the key mechanisms involves the activation of the Nuclear Factor Erythroid 2-related Factor 2 (Nrf2) pathway (Ranasinghe et al., 2022). Upon exposure to these compounds, Nrf2, a transcription factor, is triggered, prompting the expression of antioxidant and detoxifying enzymes such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD). Consequently, the upregulation of these enzymes aids in neutralizing reactive oxygen species and mitigating oxidative stress within cells (Ngo & Duennwald, 2022). Furthermore, tocotrienols, in particular, engage in the Keap1-ARE pathway. Within this pathway, tocotrienols interact with Kelch-like ECH-associated protein 1 (Keap1), leading to the activation of the antioxidant response element (ARE) through Nrf2 (Baird & Yamamoto, 2020). According to Ngo and Duennwald (2022), this activation elevates antioxidant and phase II detoxifying enzymes, which collectively serve to fortify cellular defense mechanisms against oxidative damage.

Moreover, emerging research suggests another avenue through which tocotrienols may operate, involving Peroxisome Proliferator-Activated Receptors (PPARs) (Hassan et al., 2021; Szewczyk et al., 2021). Specifically, tocotrienols have been implicated in the activation of PPAR-γ, a nuclear receptor involved in the regulation of lipid metabolism, inflammation, and oxidative stress (Qureshi, 2022). Activation of PPARs by tocotrienols may contribute to the suppression of pro-inflammatory gene expression and the promotion of antioxidant defense mechanisms, thereby further enhancing cellular resilience against oxidative insults (Muzio et al., 2021). The possible mechanisms through which tocopherols and tocotrienols orchestrate their antioxidant effects via intricate molecular pathways, including the Nrf2 pathway, Keap1-ARE pathway, and potential activation of PPARs, are presented in Fig. 5. Understanding these mechanisms sheds light on the diverse roles these compounds play in cellular protection against oxidative stress and

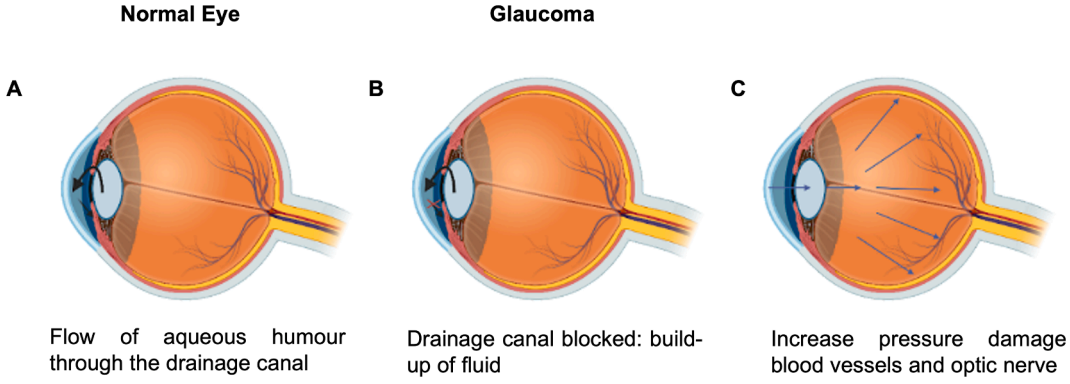


**Fig. 4.** Development of Glaucoma. Figures were adapted from Watson (2022) "The Facts About Glaucoma, Harvard Health Publishing, Harvard Medical School (2020)" and recreated by using Biorender.com. Note: (A) the first eyeball shows the condition of the normal eye, (B) the second eyeball exhibits the blockage of the canal, and (C) the third eyeball shows the elevation of intraocular pressure after the blockage occurs.

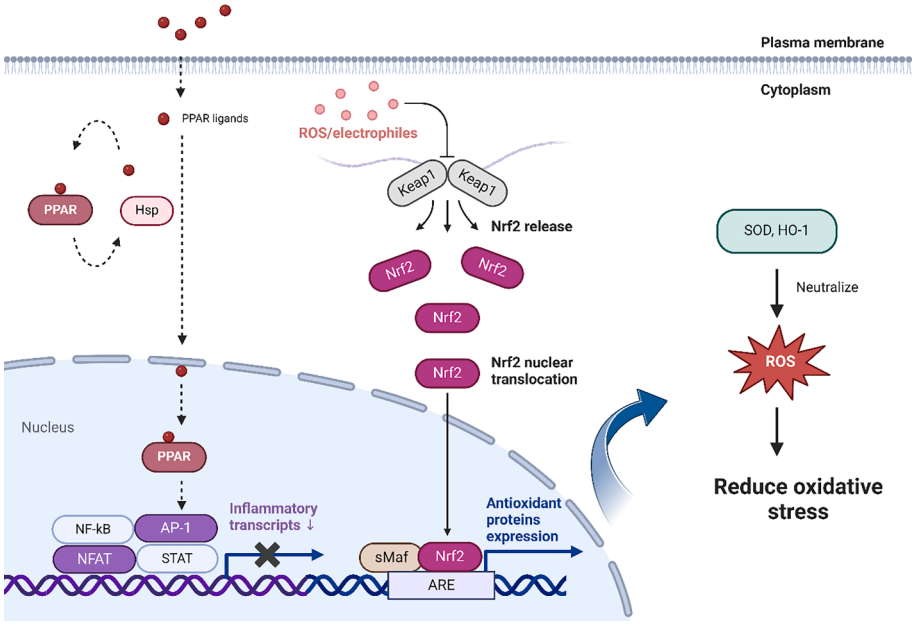


**Fig. 5.** Possible Mechanism on How Tocopherol and Tocotrienol Acts at The Cellular Level. Figure created by Biorender.com. PPAR (Peroxisome Proliferator-Activated Receptor), HSP (Heat Shock Proteins), Nrf2 (Nuclear Factor Erythroid 2-related Factor 2), AP-1 (Transcription Factor AP-1), NF-κB (Nuclear Factor NF-κB), ARE (Antioxidant Response Element), Keap1 (Kelch-like ECH-associated protein 1), HO-1 (heme oxygenase-1) and SOD (Superoxide Dismutase).

their potential therapeutic implications in combating various oxidative stress-related disorders.

## 8. Conclusion and future directions

Vitamin E is an essential nutrient found in a variety of plant-based sources such as green leafy vegetables, nuts, seeds, and plant oils. It mainly exists in two forms: tocopherols and tocotrienols. α-Tocopherol is commonly found in green leafy plants, while γ-tocopherol is more prevalent in fruits and seeds. Since its discovery in the early 20th century, Vitamin E has been celebrated for its crucial role in preventing deficiency diseases and promoting overall health. The structural differences between tocopherols and tocotrienols influence their functions in the body. Tocopherols are known for their ability to integrate smoothly into cell membranes, providing stable antioxidant protection. In contrast, tocotrienols, with their unique unsaturated side chains, can penetrate lipid bilayers more effectively, offering superior protection against oxidative stress. Interestingly, tocotrienols, despite being less bioavailable, have shown significant potential in managing chronic diseases like cardiovascular conditions and cancer. This makes them a compelling area of study. Moreover, Vitamin E's sustainability aspect is noteworthy. By recycling waste materials from its production, tocopherols and tocotrienols can be transformed into valuable resources, which not only addresses environmental concerns but also creates new economic opportunities. The therapeutic potential of Vitamin E in treating ocular diseases, such as glaucoma and cataracts, is also under investigation. While preliminary studies suggest that tocopherols and tocotrienols might reduce intraocular pressure and provide neuroprotective effects, more comprehensive clinical trials are needed. Research should also explore the potential of combining Vitamin E with existing glaucoma treatments to enhance therapeutic outcomes and study the long-term effects of Vitamin E supplementation on eye health.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT 3.5 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.

## CRediT authorship contribution statement

**Fazira Latib:** Writing – original draft. **Muhamad Arif Irfan Zafendi:** Writing – original draft, Visualization. **Mohd Aizuddin Mohd Lazaldin:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mohd Aizuddin Mohd Lazaldin reports financial support was provided by University of Technology Malaysia. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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