Nuclear factor erythroid 2-related factor 2 (Nrf2) acts as a regulator of many biological processes and plays an essential role in preventing oxidation, inflammation, and fibrosis. In the past 20 years, there has been increasing research on the role of Nrf2 and oxidative stress in human glaucoma, including the roles of inflammation, trabecular meshwork cells, retinal ganglion cells, Tenon's capsule, antioxidants, fibrosis, and noncoding RNAs. Studies have shown that the upregulation of Nrf2 can reduce damage from oxidative stress in the trabecular meshwork cells and the retinal ganglion cells, reduce fibrosis in Tenon's capsule fibroblasts, which may reduce the progression of fibrosis after surgery for glaucoma. The regulatory roles of Nrf2, microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and exogenous compounds on trabecular meshwork cells (TMCs) and retinal ganglion cells have also been studied. The use of Nrf2 agonists, including noncoding RNAs, control the expression of Nrf2 through signaling pathways that continue to be investigated to identify effective treatments to improve clinical outcome following surgery for glaucoma. This review of publications between 1999 and 2019 aims to focus on the potential mechanisms of Nrf2 in the occurrence and development of glaucoma and the prognosis following surgical treatment. Also, several factors that induce the expression of Nrf2 in trabecular meshwork cells, retinal ganglion cells, and human Tenon's capsule fibroblasts are discussed.
Background

Worldwide, glaucoma results in irreversible blindness in humans, especially in elderly individuals, and is associated with oxidative stress [1]. One of the critical risk factors of primary open-angle glaucoma (POAG) is ocular hypertension [1]. Recent studies have shown that oxidative stress is involved in the occurrence and development of POAG [2,3]. In conditions of oxidative stress, the biological defense system comes across dysfunctions and will cause an imbalance between the production and elimination of reactive oxygen species (ROS) [4,5]. Increased accumulation of ROS leads to damages to genes, proteins, and lipids [6]. These effects of oxidative stress have also been reported in corneal disease [7], cataract [8], retinal disease [9], and glaucoma [10].

According to the mechanical theory of glaucoma, studies have shown that outflow of the aqueous humor may be partially blocked by dysfunction induced by oxidative stress of trabecular meshwork cells, which results in ocular hypertension [11]. Pathologically high intraocular pressure (IOP) can further cause retinal ganglion cell mitochondrial dysfunction and apoptosis and contributes to loss of vision in patients with glaucoma [12].

Recently, the roles of nuclear factor erythroid 2-related factor 2 (Nrf2) and the associated signaling pathways in the regulation of oxidative stress responses have been studied [13,14]. Nrf2 is an important regulator of protective antioxidant and anti-inflammatory responses, which regulates the expression of many genes [15]. Nrf2 regulates not only responsive antioxidant enzymes but also a series of genes involved in processes that include inflammation, tissue remodeling, and fibrosis [16]. The Nrf2 signaling system, together with its regulatory molecules and interacting proteins, performs a critical antioxidant and anti-inflammatory function in cells. In normal conditions, Nrf2 is located in the cytoplasm and mediates proteasome degradation by binding to Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 (Keap1).

Following the initiation of cellular oxidative stress on exposure to electrophiles, including hydrogen peroxide (H₂O₂), superoxide anion (O₂⁻), hydroxyl radical (–OH), and ROS, Keap1 undergoes conformational changes. These changes allow Nrf2 to be transported into the cell nucleus to bind to the antioxidant response element (ARE) regions. Then, transcription of antioxidant enzymes and phase II detoxification enzymes occurs [17]. Also, γ-glutamyl cysteine ligase catalytic subunit (GCLC), glutathione peroxidase [13], glutathione-S-transferase (GST), catalase, superoxide dismutase, and thioredoxin uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase occurs [18–21]. However, Nrf2 may be dissociated from the cytoplasmic Nrf2-Keap1-cul3 complex by p62, which is a marker of cell autophagy [22].

Some compounds, primarily exogenous compounds, including polyphenols [23], flavonoids [24], terpenoids [25], or noncoding RNAs [26] have been reported to be Nrf2 activators or inducers. These compounds may have key roles in protecting ocular cells from oxidative stress, inflammation, and fibrosis [27,28]. The participation in the mechanism and antioxidative capacity of Nrf2 occurs in several systemic diseases, including respiratory disease [29], cardiovascular, and cerebrovascular disease [30], degenerative disease, tumors [31], and ocular disease.

This review aims to focus on the specific role and potential mechanism of Nrf2-mediated defense in glaucoma, including the prevention of oxidation and fibrosis in glaucoma. Publications have been reviewed from the past 20 years, between 1999 and 2019, with a focus on the potential mechanisms of Nrf2 in the occurrence and development of glaucoma and the prognosis following surgical treatment. Also, several factors that induce the expression of Nrf2 in trabecular meshwork cells, retinal ganglion cells, and Tenon's capsule fibroblasts are discussed.

Oxidative Stress, Glaucoma, Trabecular Meshwork Cells, and Nrf2

The trabecular meshwork is an avascular, complex connective tissue component that can effectively regulate the outflow of aqueous humor [32]. The sources of trabecular meshwork oxidative stress include ultraviolet (UV)-based byproducts of the anterior chamber, excess ROS accumulation [33], and the imbalance between oxidants and antioxidants [6,34]. Studies have shown that in patients with POAG, the trabecular meshwork is exposed to ROS in aqueous humor, which suggests that ROS may have a causative role in glaucoma at the level of trabecular meshwork cells [35,36]. As one of the most sensitive ocular cells, the trabecular meshwork cell is a primary cell type that occupies and forms the proximal portion of the aqueous humor outflow pathway. Trabecular meshwork cells under oxidative stress show changes that are typical for POAG. These changes include the accumulation of extracellular matrix (ECM), cell apoptosis, cell necrosis, changes in the structure and function of the cytoplasm and lysosomes [37], and disruption of the cytoskeletal disruption [38]. These changes may be significantly reduced using prostaglandin analogs [39], antioxidants, beta-blockers [40], or the local use of carbonic anhydrase inhibitors [41,42].

The reduction of total reactive antioxidant capacity in patients with POAG is reduced by 60–70%, which indicates that these patients might be more susceptible to damage from oxidative stress [6,43]. In 2017, Cheng et al. found that compared with normal human trabecular meshwork cells, Nrf2 expression was down-regulated in glaucomatous trabecular meshwork cells,
In 1999, Lam et al. showed that, in a retinal ganglion cell activity of Nrf2 knockout mice was reduced, indicating that Nrf2 had an inherent protective effect on retinal ganglion cells [55]. These findings support the role of Nrf2 in protecting trabecular meshwork cells from oxidative stress.

**Oxidative Stress, Glaucoma, Retinal Ganglion Cells, and Nrf2**

Retinal ganglion cells are specialized neurons that receive visual information from photoreceptor cells [46]. Retinal ganglion cells transmit visual information to the brain in the form of neural activity [53]. Chronic hypertension, age-related macular degeneration, and diabetic retinopathy, oxidative stress results in cell death of retinal ganglion cells [9,27].

The potential mechanisms involved in cell death of retinal ganglion cells in glaucoma and disorders of optic nerve blood flow have been studied [47]. These mechanisms include excitatory glutamate toxicity [48], and injury due to the effects of nitric oxide [49]. Recently, studies have shown that vascular and mechanical processes that include pro-apoptotic factors can result from oxidative stress leading to oxidative mitochondrial dysfunction in retinal ganglion cells and apoptosis during acute glaucoma [50–52].

Based on the vascular theory of glaucoma, reactive oxygen species (ROS) are produced by ischemia. The mechanical theory of glaucoma proposes that ROS formation results from increased intraocular pressure (IOP) and inhibition of axons of retinal ganglion cells [53]. Chronic hypertensive glaucoma and retinal ischemia caused by a sudden increase in IOP stimulate the production of ROS and dysregulate essential autophagy [50]. With a chronic retinal injury or a sudden and severe increase in IOP, cell autophagy increases that result in oxidative mitochondrial dysfunction in retinal ganglion cells and apoptosis during acute glaucoma [50–52].

In 2015, Xu et al. reported that Nrf2 had a role in retinal neuroprotection from ischemia-reperfusion injury [55]. These investigators developed and studied an Nrf2 knockout mouse retinal ischemia-reperfusion model [55]. When compared with wild-type mice, the loss of neurons in the retinal ganglion cell layer in the Nrf2 knockout mice was increased, and the retinal ganglion cell activity of Nrf2 knockout mice was reduced, indicating that Nrf2 had an inherent protective effect on retinal ganglion cells [55]. In 1999, Lam et al. showed that, in a rat model, repeated mild retinal reperfusion resulted in chronic oxidative stress, especially in cell mitochondria [56]. Virus-mediated delivery of Nrf2 can effectively protect retinal ganglion cells from damage due to oxidative stress after acute nerve damage [57]. Therefore, pharmacologic and physiological induction of Nrf2 has potential as a new therapeutic strategy for retinal ischemia-reperfusion damage, and possibly for other retinal diseases, including glaucoma.

**Fibrosis, Nrf2, and Tenon’s Capsule Cells**

Fibrosis is part of the healing process that follows inflammation in many diseases, including lung disease, liver fibrosis [58], systemic sclerosis [59], and diabetic renal fibrosis [60]. The mechanisms leading to fibrosis can involve stress responses involving the endoplasmic reticulum (ER) [61], oxidative stress [62], and inflammation [63]. Trabeculectomy, a traditional method of glaucoma filtration surgery, is regarded as one of the most effective strategies to achieve a sustained reduction in IOP in patients with glaucoma [64]. Glaucoma filtration surgery destroys the structure of the conjunctiva and subconjunctival tissue, activates the immune system, and results in the release of inflammatory cytokines [65]. Platelet activation and inflammatory cytokines activate downstream vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and platelet-derived growth factor (PDGF) [66]. Inflammatory cytokines and growth factors induce cell proliferation, cell migration, the accumulation of extracellular matrix (ECM), and results in the contraction of collagen to promote scar formation, which results in impaired surgical outcomes in patients with glaucoma [66].

TGF-β1 causes cell apoptosis [67], the expression of genes associated with fibrosis, and myofibroblast differentiation following the production of ROS [68]. TGF-β1 also inhibits the glutathione antioxidant system [69]. The miRNA-29 family is closely associated with TGF-β-mediated fibrosis [70,71]. In patients with glaucoma, TGF-β2 was shown to stimulate fibroblast proliferation in Tenon’s capsule by the suppression of miR-29b expression regulated by Nrf2 [72]. These findings indicate that Nrf2 may protect cells from the effects of TGFβ and fibrosis by upregulating miR-29b. Long noncoding RNA (IncRNA)-MEG3 upregulates the expression of Nrf2 and controls the proliferation of ECM [73]. These findings support that Nrf2 might be a potential therapeutic target to prevent fibroblast proliferation in Tenon’s capsule after glaucoma filtration surgery.

**Novel Strategies for Activating Nrf2: Noncoding RNAs**

MicroRNAs (miRNAs) are small noncoding RNAs of between 19–25 nucleotides in length that regulate a wide range of
Table 1. The regulatory roles of nuclear factor erythroid 2-related factor 2 (Nrf2), microRNAs (miRNAs), and long noncoding RNAs (lncRNAs).

| miRNA     | Cell type                     | Functions                                                                 |
|-----------|-------------------------------|---------------------------------------------------------------------------|
| miR-29b   | Tenon’s capsule fibroblasts   | TGF-β2 stimulates fibroblast proliferation by suppression of miR-29b expression regulated by Nrf2 [89] |
| miR-93    | Trabecular meshwork cells     | Inhibits the viability and induces apoptosis of the trabecular meshwork cells by the inhibition of Nrf2 [43,45] |
| miR-141   | Retinal ganglion cells        | Reduces ultraviolet (UV) light-induced oxidative stress via the activation of Keap1-Nrf2 signaling [90,91] |
| IncRNA-MEG3 | Tenon’s capsule fibroblasts | TGF-β2 induces proliferation by binding MEG3 to Nrf2 [73,92] |

Table 2. The regulatory role of nuclear factor erythroid 2-related factor 2 (Nrf2) and exogenous compounds on trabecular meshwork cells (TMCs) and retinal ganglion cells (RGCs).

| Name                  | Target          | Type of study                      | Functions                                                                 |
|-----------------------|-----------------|-----------------------------------|---------------------------------------------------------------------------|
| Quercetin             | TMCs            | Fruit, vegetables, and dietary sources, using conventional doses or nanodoses | Upregulates antioxidant peroxiredoxins through the Nrf2 pathway [93]        |
| Lipoic acid           | RGCs            | A disulfide compound found both naturally in mitochondria or in pharmaceutical form | Induces HO-1 by promoting the translocation of Nrf2 to the cell nucleus [94–96] |
| Sulfurophane (SFN)    | TMCs & RGCs     | Broccoli sprouts, other cruciferous vegetables, or food supplements          | Reduces H2O2-induced oxidative stress via PI3K/Akt-mediated Nrf2 signaling activation [97,98] |
| CDDO-Im               | 661W cells      | A synthetic triterpenoid compound                                           | Inhibits ROS and increases neuronal cell survival after ischemia-reperfusion injury [55] |
| 1R-iso Proplyoxy genipin (IPRG001) | RGCs | A long-acting synthetic compound.                                           | The protective action depends on NO induction and the Nrf2/HO-1 antioxidant response element pathway by S-nitrosylation [99]. |
| Resveratrol           | RGCs            | Grapes, peanuts, red wine, cocoa, berries, or pharmaceutical form            | Upregulates the expression of Nrf2, HO-1, and NQO1 [100,101]              |
| L-carnitine (LC)      | RGCs            | Endogenous biosynthesis and dietary sources, or in pharmaceutical form      | Increases levels of Nrf2, ho-1, and γ-GCS, and decreases expression of Keap1 protein [9] |
| SNJ-1945 – an exogenous calpain inhibitor | RGCs | In pharmaceutical form                                                      | Protects RGCs against OS induced by high glucose [102]                     |
| Monomethyl fumarate (MMF) | Ganglion cell layer | In pharmaceutical form.                                                     | Protects neuronal function via Nrf2 modulation [103].                    |
| Trimetazidine         | RGCs            | In pharmaceutical form                                                       | Confers protection against RGC apoptosis via Nrf2/HO-1 signaling [104]  |
| Hydrogen sulfide (H₂S) donor drugs | RGCs | In pharmaceutical form                                                       | Increases the levels of Nrf2, HO-1, and inhibits oxidative stress-induced cell death [105]. |
| 5α-and rost-3β, 5α, 6β-triol (TRIOL) | RGCs | A synthetic compound                                                         | Activates and upregulates Nrf2, HO-1, by negative regulation of Keap1 [106] |
Table 2 continued. The regulatory role of nuclear factor erythroid 2-related factor 2 (Nrf2) and exogenous compounds on trabecular meshwork cells (TMCs) and retinal ganglion cells (RGCs).

| Name                  | Target     | Type of study               | Functions                                                                 |
|-----------------------|------------|-----------------------------|---------------------------------------------------------------------------|
| Nipradilol            | RGCs       | In pharmaceutical form      | Protects RGCs through S-nitrosylation of Keap1 and HO-1 induction [107]    |
| Flavonoids            | RGCs       | Fruits, vegetables or food supplements | Induces Nrf2 and HO-1 [108]                                               |
| Sulbutiamine          | RGCs       | Sulbutiamine (Arcalion 200®) | Stimulates catalase and increases Nrf2 and HO-1 levels [109]               |
| L2H17, a chalcone analog | RGCs       | A synthetic compound        | L2H17 exhibits antioxidative effects by activating the Nrf2 pathway [110]   |
| Chlorogenic acid      | RGCs       | In food or food supplements | Reduces oxidative injury through IncRNA-TUG1/Nrf2 [111]                   |

TMCs – trabecular meshwork cells; RGCs – retinal ganglion cells; HO1 – heme oxygenase-1; ROS – reactive oxygen species; NO – nitric oxide.

processes by targeting genes [6]. Long noncoding RNAs (IncRNAs) are >200 nucleotides in length that regulate transcription (cis or trans), the organization of nuclear domains, and RNA or protein formation through several different mechanisms [6,74,75]. Recently, noncoding RNAs have become a focus of glaucoma research, as shown in Table.1. Noncoding RNAs provide a potential therapeutic approach for defense against oxidative stress and fibrosis in glaucoma.

Novel Strategies for Activating Nrf2: Exogenous Compounds

There are several compounds that have anti-inflammatory, antioxidant, and properties that prevent fibrosis by directly targeting the Nrf2 and Nrf2 inhibitors that include Keap1, Bach1, c-Myc, with the potential for preventing ocular disease [76–78]. There has been increasing interest in studies on the role of exogenous compounds to prevent oxidative stress. Compounds that include chalcones, flavonoids, and terpenoids can suppress Nrf2 ubiquitination and induce ARE-mediated antioxidative and cytoprotective enzymes [79]. These proteins react with the cysteine thiolate groups in Keap1, which are typical Nrf2 inducers [79]. Also, phenols and quinones, such as t-BHQ [80], polyphenolic flavonoids, including quercetin [81], stilbenoid, and nonflavonoid polyphenolics, including resveratrol [82] have been studied. Other compounds include sulforaphane (SFN), sphaeropsidin A (SA), CDDO-Im, long-acting (1R)-isopropylxoygenipin (IPRG001), omaveloxolone, astaxanthin [83], and lycopene [84], which also show activation of Nrf2 and upregulation of some downstream Nrf2 genes. Table 2 summarizes the studies on Nrf2 activators associated with glaucoma and neuroprotection.

The Negative Effects of Nrf2 in Glaucoma

Although Nrf2 has many protective effects in oxidative stress, studies have shown that Nrf2 can have harmful effects, including as a carcinogen, as cancer-associated mutations activate Nrf2 [85–87]. Also, when ROS exceeds the critical threshold, Nrf2 upregulates the expression of Klf9. However, Klf9 inhibits Trx reductase expression, amplifying the ROS cascade, which ultimately leads to cell death [88]. Therefore, it is important to consider the beneficial effects of Nrf2 as well as the harmful effects.

Conclusions

In the past 20 years, studies have shown that Nrf2 has a role in the occurrence and development of glaucoma and the prognosis following surgical treatment. Also, several factors that induce the expression of Nrf2 in trabecular meshwork cells, retinal ganglion cells, and human Tenon’s capsule fibroblasts. Nrf2 plays a specific role in the occurrence and development of glaucoma. Oxidative stress accounts for some of the main mechanisms of trabecular meshwork cell injury, apoptosis, aqueous humor outflow disorders, and the loss of structure and function of retinal ganglion cells. Also, Nrf2 has a role in preventing fibrosis after glaucoma filtration surgery. Therefore, Nrf2 might be a potential therapeutic target to protect ocular cells from oxidative stress.

Conflict of interest

None.
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