Research progress on antioxidants and protein aggregation inhibitors in cataract prevention and therapy (Review)

LING WANG[1,2*], XIN LI[1,2*], XIAOJU MEN[1], XIANGYI LIU[1] and JINQUE LUO[1]

[1]Hunan Provincial Key Laboratory of The Research and Development of Novel Pharmaceutical Preparations, Changsha Medical University, Changsha, Hunan 410219, P.R. China; [2]Hunan Provincial University Key Laboratory of Fundamental and Clinical Research on Neurodegenerative Diseases, Changsha Medical University, Changsha, Hunan 410219, P.R. China

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Abstract. Cataracts are primarily caused by aging or gene mutations and are the leading cause of blindness globally. As the older population increases, the number of patients with a cataract is expected to grow rapidly. At present, cataract surgery to replace the lens with an artificial intraocular lens is the principal treatment method. However, surgery has several drawbacks, including economic burdens and complications such as inflammation, xerophthalmia, macular edema and posterior capsular opacification. Thus, developing an effective non-surgical treatment strategy is beneficial to both patients and public health. Mechanistically, cataract formation may be due to various reasons but is primarily initiated and promoted by oxidative stress and is closely associated with crystallin aggregation. In the present review, the current research progress on anti-cataract drugs, including antioxidants and protein aggregation inhibitors is examined. It summarizes strategies for preventing and treating cataract through cell apoptosis and protein aggregation inhibition while discussing their limitations and further prospects.

Contents

Correspondence to: Dr Jinque Luo, Hunan Provincial Key Laboratory of The Research and Development of Novel Pharmaceutical Preparations, Changsha Medical University, 1501 Leifeng Avenue, Changsha, Hunan 410219, P.R. China
E-mail: luojinque2019@hotmail.com

*Contributed equally

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1. Introduction

Lens opacification, also termed cataract, is among the leading causes of vision loss worldwide, and has resulted in blindness in at least 53 million individuals globally at present (1,2). Cataract phacoemulsification followed by intraocular lens implantation is the current sole treatment for this ailment (3). However, cataract surgery is a great burden on global health-care and individuals. Firstly, as the global population ages, the number of cataracts are expected to increase, which will place an even heavier social and economic burden on healthcare (4). Unfortunately, expenses and the overall medical condition limit surgery for numerous individuals. For example, in China, the ophthalmologists are concentrated in eastern urban areas (5) and the current cost of cataract surgery is too expensive for numerous individuals (6). Second, patients may undergo complications after cataract surgery, such as inflammation, xerophthalmia, macular edema or even posterior capsular opacification (PCO) (4), which greatly affects wellbeing. PCO is the most common complication and when it occurs, it can lead to secondary vision loss or blindness in 30-50% of adults and in 100% of children (7). Therefore, elucidating the changes that cause cataracts and developing pharmacological preventative and therapeutic strategies is crucial.

Eye lenses are optically clear structures behind the iris and in front of the vitreous body that focus light on the retina (8). Lenses are formed from ectodermal tissue and are comprised of lens epithelium and lens fibers (9). The lens epithelium is one single layer of anterior epithelial cells and, during lens development, the lens epithelial cells gradually migrate towards the lens equator, where they invert and elongate to differentiate into fiber cells (10). Meanwhile, differentiating cells synthesize large amounts of soluble lenticular proteins, including crystallins, while degrading their organelles and nuclei to increase lens transparency (10). Any disturbances in the lens epithelium or lens fibers will result in a loss of lens transparency (11).

There are two major types of cataract (12). First, senile cataracts are age-related and are the most common (12). Age-related lens changes are primarily caused or accelerated by oxidative stress, UV, osmotic or other damaging factors including smoking and undernutrition (13). When a senile cataract develops, the lens undergoes numerous biochemical

and biophysical changes, such as an increase in insoluble crystallin proteins and a buildup of free radical-associated damage to lens constituents; both of which will result in lens transparency loss (14). The second is congenital cataracts, which are present at birth or during early childhood and are less common but can cause complete blindness in children (12,15). Congenital cataracts are the primary cause of vision loss in children worldwide (16) and have a diverse etiology, with inheritance of genetic mutations being the most common cause (17). In total, >30 causative genes have been shown to be related to congenital or other early-onset forms of cataract such as progressive juvenile cataracts (18). Furthermore, medical conditions such as diabetic injuries or other eye diseases such as uveitis, retinitis pigmentosa may also cause cataractogenesis (12,19). The pharmacological prevention and treatment strategy for cataracts of any type is not well established. Therefore, the present review examines the literature regarding the recent progress on pharmacological prevention and therapy for cataracts (Fig. 1).

2. Antioxidants

It is well established that oxidative stress causes cataract development (19). Under certain conditions such as radiation, smoking and malnutrition, reactive oxygen species (ROS) accumulate in the lens, which cause damage (20). The cellular ROS components, including superoxide anion (O_2•), hydroxyl ion (OH•) and hydrogen peroxide (H_2O_2) (21), can damage proteins in the cytoplasm and phospholipids in the cellular membrane (22,23). Free radicals cause the formation of lipid oxidation and primary lipid peroxidation (LPO) products such as malondialdehyde (MDA), which accumulate during cataract development (24-26). Furthermore, the generated LPO end-products are closely associated with the degree of lens opacity (27). By contrast, lens cells have different mechanisms to protect themselves against oxidative stress including scavengers such as glutathione (GSH) and antioxidant enzymes such as superoxide dismutase (SOD) and cytosolic glutathione-S-transferase (28). In the aging lens, there is an accumulation of oxidative damage, which is produced by ROS that are generated by factors such as UV exposure and hyperglycemia (29). The endogenous protection systems such as neutralizing agents, antioxidants and antioxidant enzymes cannot counteract the excessive oxidative stress (29). Disruption of the redox equilibrium promotes oxidative damage and thus, the aggregation of proteins that lead to the loss of the transparency of the lens (29). Therefore, antioxidants are recommended to prevent, postpone and treat cataractogenesis (28). However, experimental research has demonstrated that while most antioxidants are effective in preventing or slowing down cataract formation, only N-acetylcarnosine has been shown to aid in the restoration of vision to some extent (30).

Multivitamins. The natural compounds, vitamins C and E, are well-known antioxidants (31). Meta-analyses have revealed that vitamin C and E intake is inversely associated with senile cataract risk (32,33). These vitamins are proven to be capable of preventing free radical generation and LPO (28). The antioxidative and anti-cataract activities of vitamins C and E have been well studied.

Vitamin C is essential for humans and is abundant in the human lens, with the human ocular humors containing 50-fold more vitamin C than plasma (34,35), which protects the lens from UV light and other damage by reacting with free radicals (36). In aged human lenses, vitamin C levels are greatly decreased and thus may fail to protect the lenses against oxidative stress-induced cataracts (37). Vitamin C supplementation has been revealed to help replenish and restore endogenous vitamin C against cataract formation (33,38). Under oxidative stress conditions, vitamin C prevents membrane LPO (39) and Na^+K^+-ATPase pump damage in the lens (40). Na^+K^+-ATPase-mediated ion transport is crucial for maintaining the correct concentration of sodium in the lens, and an abnormal elevation of lens sodium has been implicated in the development of senile cataracts (41). *In vitro*, the physiological concentration of vitamin C protects lens cells and dissected lenses against H_2O_2 (42), UVB exposure (43) and other ROS-inducing factors such as hyperglycemia (44), and thus against induced oxidative damage. An *in vivo* study by Devamanoharan *et al* (45) found that a 0.3 mM per rat pup/day intraperitoneal vitamin C injection maintained ATP and GSH levels and decreased MDA (the end product of LPO) levels to prevent nuclear cataract development. ATP, the intracellular energy currency molecule, has been shown to act as a biological hydrotrope to prevent pathological protein aggregation and maintain protein solubility (46), while elevated MDA levels are associated with cataract formation (47). Additionally, a 1% (w/w) dietary intake of vitamin C has been shown to reduce cataractogenesis in streptozotocin (STZ)-induced diabetic rat models by decreasing γ-crystallin leakage (48,49) and relieving oxidative stress by increasing GSH peroxidase (GSH-Px) activity and reducing peroxidation levels (50).

However, under pathological or overdose conditions, vitamin C can switch from being an antioxidant to a pro-oxidant, suggesting a role in stimulating the progression of cataracts. First, a high concentration of vitamin C (1 M) has been reported to promote the Fenton reaction, thus contributing to the formation of hydroxy radicals as well as dehydroascorbic acid (DHA) and H_2O_2, which are toxic to the lens (51). DHA is a reactive electrophile and the primary oxidation product of vitamin C (51). DHA levels increase in response to oxidative stress and are hypothesized to be associated with various ROS and protein glycation-related diseases, including senile cataracts (52). Similar to oxidation, glycation is a deleterious form of post-translational modification that is linked to age-related diseases, particularly cataracts (53). The accumulated glycation of proteins in the lens may induce protein conformational changes that stimulate further glycation and oxidation as well as trigger protein aggregation leading to a cataract (54). 2,3-diketo-L-gulonic acid (2,3-DKG) is the further degradation product of DHA, and a heightened level of 2,3-DKG has been shown to be related to increased cataractogenesis *in vivo* (55). Vitamin C or its breakdown products react with their substrate proteins to accelerate cataract development. Fan *et al* (56) reported that vitamin C acts as a chaperone of methylglyoxal hydroimidazolones, enhancing oxoaldehyde stress, which promotes senile cataract progression. Additionally, incubation of vitamin C and individual crystallins results in the glycation and cross-linking of isolated lens crystallins (57). Furthermore, L-erythrulose,

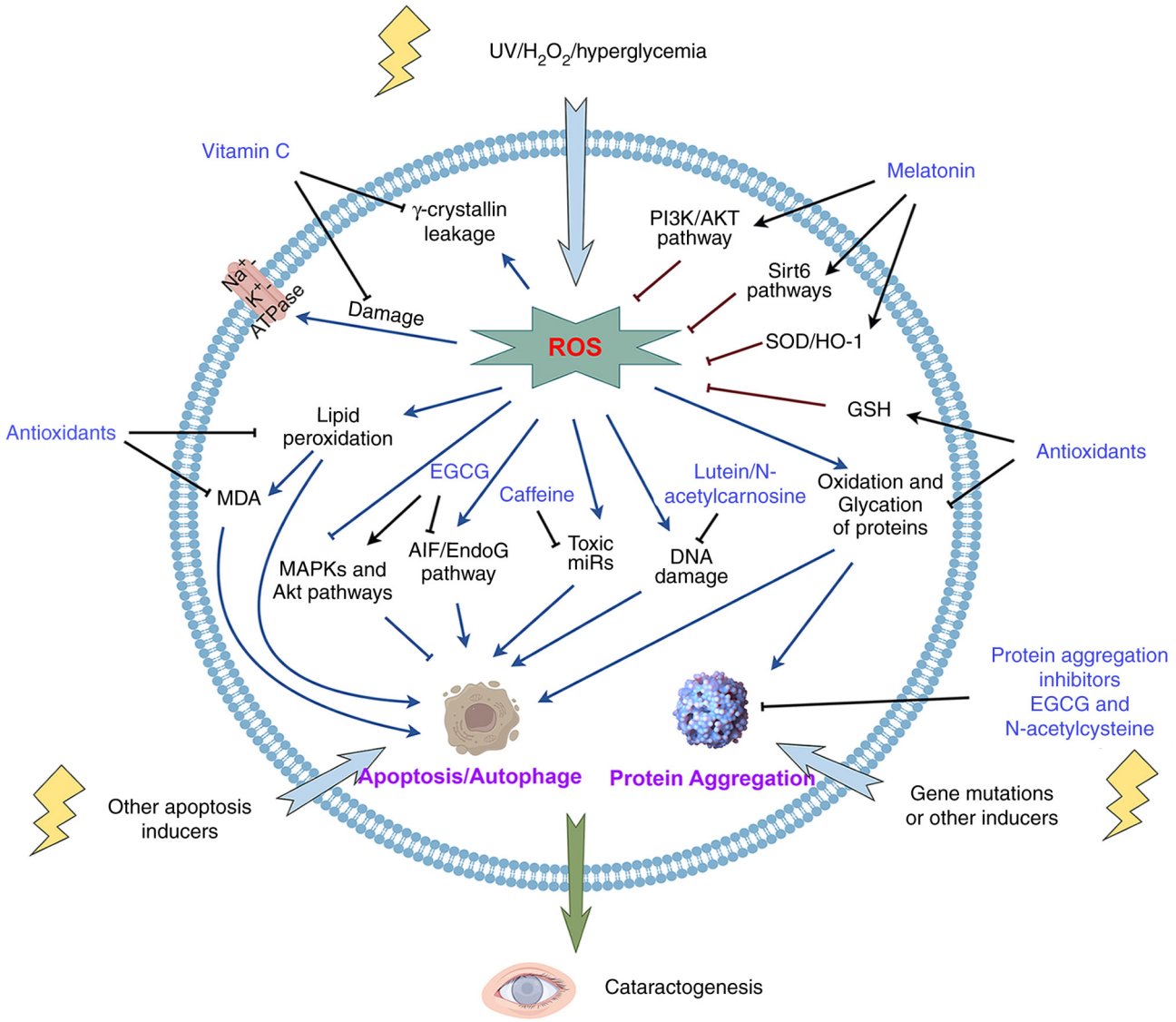

Figure 1. Mechanisms of antioxidants and protein aggregation inhibitors in cataract prevention and therapy. SOD, superoxide dismutase; HO-1, heme oxygenase-1; EGCG, epigallocatechin-3-gallate; MDA, malondialdehyde; AIF/EndoG, apoptosis-inducing factor/endonuclease G; GSH, glutathione; ROS, reactive oxygen species.

which induces protein glycation and cross-linking, has been identified as the major non-oxidative degradation product of vitamin C and participates in diabetic and age-onset cataract formation (51). Overall, the existing experimental data suggest that an appropriate level of vitamin C is essential to protect the lens from oxidative damage. By contrast, boosting vitamin C levels could be toxic to the lens and result in cataract formation.

Similar to vitamin C, vitamin E has also been identified as an antioxidant that protects against oxidative stress-associated eye diseases such as cataracts and glaucoma (58). It has been shown that higher levels of vitamin E are associated with lower cataract risk (59), while a reduced vitamin E concentration is relevant to the development of senile cataracts (60). Lens organ culture studies have shown that the lipid solubility and antioxidant capabilities of vitamin E shield membranes and scavenge free radicals to reduce cataractogenesis (61-63). Animal studies have also confirmed the protective effects of vitamin E on the lens. First, vitamin E has been reported to prevent hyperglycemia-induced oxidative stress and cataractogenesis by restoring GSH and reducing the formation of MDA in the lenses of diabetic transgenic mice (64). Vitamin E has also been shown to prevent cataracts induced by ionizing radiation (65), steroids (66), UV radiation (67) or selenite (68). Furthermore, a randomized human lens sample study involving 50 patients with unilateral/bilateral idiopathic immature senile cataracts showed that patients receiving vitamin E had higher levels of reduced GSH and GSH-Px as well as lower levels of MDA and lens opacity in the cortical cataractous lenses compared with the placebo group (69), directly confirming the protective effect of vitamin E in the human lens.

Carotenoids. Carotenoids, a naturally occurring group of lipo-soluble pigments, are potent antioxidants that neutralize and scavenge free radicals (70). This group comprises >600 natural compounds, among which lutein and its stereoisomer, zeaxanthin, were revealed to assist in preventing and mitigating oxidative-induced cataracts (71,72). Additionally, lutein/zeaxanthin has been found to neutralize or reduce

free radicals in the human lens and filter against high-energy and harmful blue light (73,74). Oxidized proteins, LPO and DNA damage increase in human lens epithelial cells in response to oxidative stress (75). However, pre-culture with 5 mM lutein/zeaxanthin has been shown to notably prevent such alterations (71), suggesting it may lessen the incidence of senile cataracts by reducing oxidative stress. Chitchumroonchokchai *et al* (76) found that 0.25 μM lutein protected human lens epithelial cells from UV-induced oxidative stress by inhibiting JNK and p38 activation. Both of which are implicated in oxidative stress inhibition and lens cell protection (77). Furthermore, experimental evidence shows that by filtering the high-energy and harmful blue light, lutein attenuates photo-induced oxidation of lens proteins, thereby protecting against age-related eye diseases, including cataracts (74). More notably, *in vivo* studies have demonstrated that lutein could counteract certain types of cataracts. Specifically, Kinoshita *et al* (78) found that 10 mg/kg/day lutein administered orally for 29 days ameliorated cataracts in type 1 diabetic rats by inhibiting the accumulation of N^{ε}-(carboxymethyl) lysine and N^{ε}-(carboxyethyl) lysine in the serum. N^{ε}-(carboxymethyl) lysine and N^{ε}-(carboxyethyl) lysine are glycoxidation products and are significantly increased by diabetes, with the typical complication being cataracts in both rats and humans (78). Combined with insulin, oral administration of 0.5 mg/kg lutein has been demonstrated to prevent the development of cataracts in STZ-induced diabetic rats by preventing the diabetes-induced reduction of GSH levels (79). A clinical trial observation also suggested that a higher dietary intake or higher blood levels of lutein/zeaxanthin are associated with a lower incidence and a slower progression of cataracts (80).

Besides its antioxidant properties, lutein inhibits bovine lens epithelial cell growth and migration *in vitro*, protecting the post-operative lens following phacoemulsification (81). Considering that fibrotic responses after surgery could result in blindness, this study demonstrates the prospects of lutein in preventing PCO.

Polyphenols. Polyphenols are the biggest group of phytochemicals, which comprise >1,000 different compounds (82). Numerous polyphenols are linked to health benefits such as antioxidant, anti-inflammatory or antiviral activities (82). Moreover, recent studies have described new findings regarding polyphenols, such as (-)-epigallocatechin-3-gallate (EGCG) and resveratrol, in lens protection.

EGCG is a primary component of green tea and has a polyphenolic structure as well as a strong antioxidant capacity to inhibit ROS generation by scavenging free radicals and chelating metal ions (83). An *in vitro* study has shown that 50 μM EGCG protects lens epithelial cells against oxidative stress-induced apoptosis by activating the MAPK and Akt pathways (84) as well as UVB irradiation-induced apoptosis through the apoptosis-inducing factor/Endonuclease G signaling pathway (85). Crystallin is a major structural protein present in the lens and its aggregation results in an augmentation of lens opacity (86). EGCG also inhibits crystallin aggregation, particularly αA (66-80), a major fragment of αA-crystallin (87) and γB-crystallin (88), which protects the lens in a concentration-dependent manner from 0 to 50 mM. In response to hyperglycemia, EGCG suppresses the high glucose-induced expression of apoptotic genes, c-Fos, c-Myc and p53 to protect human lens epithelial cells, suggesting a protective role of EGCG in diabetic cataract formation (89). Furthermore, an *in vivo* study confirmed that oral administration of 1 mg/kg EGCG prevented lens opacity and αB-crystallin aggregation in diabetic rat models (90). Although EGCG is a redox-active molecule, it auto-oxidizes to produce superoxide radicals and H_2O_2 (91). Contradictory data demonstrate that a high level of EGCG (200 mM) inhibits lens epithelial cell growth and induces apoptosis (92,93), indicating its use in PCO prevention.

Resveratrol, another natural polyphenol, is a radical-scavenging antioxidant and anti-aging agent (94). Accumulating evidence has demonstrated that resveratrol has a therapeutic and preventive effect on the eye, specifically the lens (95). *In vitro* research has revealed that resveratrol protects human lens epithelial cells against oxidative stress in a concentration-dependent manner by enhancing catalase, SOD-1 and heme oxygenase-1 (HO-1) expression (96), and activates autophagy to protect cells against high glucose-induced oxidative stress (97). Both HO-1 and its upstream regulator, nuclear factor erythroid 2-related factor 2 (Nrf2), are oxidative stress inhibitors (98-100). Autophagy refers to the physiological and pathological processes of cellular lysosomal degradation, which are not only essential for cell survival and development but are also associated with various human diseases including diabetes (101-103). The activation of autophagy has been reported to protect against oxidative stress and apoptosis under specific conditions (104,105). Resveratrol has also displayed a protective role in animal models. First, in STZ-induced diabetic rats, Singh *et al* (106) and Higashi *et al* (107) found that oral administration of 40 mg/kg/day resveratrol is beneficial in the pharmacotherapy of diabetes and its secondary complications, such as cataracts, through the attenuation of oxidative damage to lens proteins. Second, Chen *et al* (108) designed a nanosystem of gold nanoparticles containing resveratrol (RGNPs). In the selenite-induced cataract model, subcutaneous injection of RGNPs improved lens opacity and decreased the mRNA and protein levels of proteins associated with the lens (γA-crystallin and βA1-crystallin) senescence markers (p16 and p21) and the activated Sirtuin (Sirt) 1/Nrf2 pathway. These findings demonstrated the anti-aging and anti-cataract effects of resveratrol (108). Resveratrol also has been shown to be a candidate agent in preventing PCO. In FHL124 cells and human lens capsular bags, 30 μM resveratrol significantly inhibited cell growth, migration and epithelial-mesenchymal transition (EMT), which are pivotal events for PCO development (109).

Melatonin. Melatonin, an amphiphilic tryptophan-derived indolamine, is primarily secreted by the pineal gland and regulates circadian rhythm (110,111). This hormone also acts a highly potent antioxidant by activating GSH synthesis and scavenging free radicals as well as an anti-inflammatory factor by functioning as an immune modulator (112). It has been demonstrated that melatonin is synthesized within the eye to counteract age-related ocular diseases including glaucoma, age-related macular degeneration, diabetic retinopathy and cataract (113). In human lens epithelial cells, 50-250 μM

melatonin decreases H_2O_2-induced intracellular ROS generation by activating the PI3K/Akt signaling pathway (114) and inhibits UVB-promoted ferroptosis by regulating two Sirt6 (Nrf2 or nuclear receptor coactivator 4) pathways (115,116). PI3K/Akt signaling has a critical role in lens protection by mediating apoptosis (117), while Sirt6 is a chromatin regulatory protein that also plays a role in combating oxidative stress (115). An *in vivo* study confirmed that melatonin delayed the development of senile cataract by activating Sirt6 (115). In an STZ-induced diabetic rat model, intraperitoneal injection of 5 mg/kg/day melatonin reduced cataract formation by increasing the GSH levels and decreasing the activity of aldose reductase (AR) and the MDA level (118). AR is the crucial enzyme in the polyol pathway and mediates the conversion of glucose to sorbitol (119,120). Accumulation of sorbitol in the lens results in osmotic trauma and eventually lens opacification (121). A study by Karslioğlu *et al* (122) revealed that melatonin protects against radiation-induced cataract by significantly increasing the activity of SOD enzymes and decreasing the MDA level. As demonstrated by the aforementioned studies, melatonin may be a promising candidate in cataract management.

Caffeine. Caffeine, a widely used drug as well as a dietary constituent, has been identified as a ROS scavenger against cataract formation. Firstly, in 2008, Varma *et al* (123) evaluated the effect of caffeine on cultured and UV radiation-exposed mice lenses and revealed that caffeine significantly maintained the active transport activity, GSH levels and transparency of lenses. Following this study, the same group then demonstrated that 5.15 μM intraperitoneally injected or a 1% dietary intake of caffeine also had a positive effect on preventing selenite-induced (124) and high sugar-induced (125) cataracts in animal models. A further study in humans revealed that a higher level of coffee consumption was co-related to a lower incidence of cataract blindness (125,126). Mechanistically, the caffeine effect could be multifactorial. First, as an antioxidant, caffeine is an effective inhibitor of LPO and against all three reactive species that cause membrane damage *in vivo*, including OH•, peroxyl radical (ROO•) and singlet oxygen ($^1O_2$), at certain concentrations (127). Caffeine also retains lens GSH and ascorbic acid levels which were significantly lower in high-fat diet-induced mice (128). Moreover, caffeine suppresses the high-galactose diet-induced elevation of toxic microRNAs particularly miR-16, miR-32, miR-218 that are known to induce apoptosis and cell death by gene silencing to prevent the formation of cataracts (125,129). Overall, caffeine is a promising candidate molecule for cataract prevention and treatment. However, excessive maternal caffeine exposure (100 mg/kg/day, intraperitoneally) during pregnancy has been indicated in inducing cataracts (130), suggesting that caution when consuming a high quantity caffeine is necessary for pregnant women.

N-acetylcarnosine. *N*-acetylcarnosine, a natural histidine-containing dipeptide, has been applied as an eye drop to prevent or reverse the progression of cataracts. N-acetylcarnosine, a prodrug, is metabolized into L-carnosine in the front chamber of the eye (131). L-carnosine is an *in vivo* universal antioxidant and has a potent protective effect against oxidative stress but cannot penetrate the cornea (131). Clinical trials have revealed that an *N*-acetylcarnosine lubricant eye drop treatment significantly improves visual function. First, an observation by Babizhayev *et al* (30) revealed that a short-period administration of *N*-acetylcarnosine lubricant eye drops rejuvenated the visual functions of older adult drivers and drivers with cataracts. Second, a clinical experiment with >50,000 participants showed that *N*-acetylcarnosine eye drops improved senile cataracts and visual acuity in patients with diabetic ocular complications (53,132,133). Mechanistically, the effect of *N*-acetylcarnosine/L-carnosine on preventing or delaying cataract formation may be through the anti-glycation of proteins, antioxidative impairment, protecting proteins against cross-linking and DNA damage (53,132,133). Protein glycation is also one of the main factors contributing to diseases such as diabetes mellitus, carcinoma and cataracts (53,134). It induces lens protein structural changes that result in protein crosslinks, aggregation and high molecular weight protein formation (135). Another study found that *N*-acetylcarnosine decreased lens cell telomere shortening to protect against oxidative stress (75,136) and the harmful effects of lipid peroxides on the crystalline lens *in vivo* (137). Taken together, *N*-acetylcarnosine/L-carnosine prevents and treats senile cataracts and is a potentially effective and non-surgical anti-cataract therapy.

N-acetylcysteine. *N*-acetylcysteine, the acetylated form of L-cysteine, has antioxidant effects and may prevent cataracts. Jain *et al* (138) first revealed that 1 mM *N*-acetylcysteine may protect lens proteins from oxidation and aggregation, which result from high blood glucose-induced oxygen radicals. Furthermore, Zhang *et al* (139) confirmed that 0.05% *N*-acetylcysteine eye drops act as a precursor of GSH biosynthesis and protect sulfhydryl groups from oxidation to inhibit diabetic cataract progression in STZ-induced diabetic rats. *N*-acetylcysteine also reportedly protects against triamcinolone acetonide, selenite and hyperoxia-induced cataractogenesis *in vivo* (140-142), which confirms the antioxidative effect of *N*-acetylcysteine in lens protection. Moreover, *N*-acetylcysteine amide is a variant of *N*-acetylcysteine that has similar or even stronger antioxidant properties than *N*-acetylcysteine (143). *N*-acetylcysteine amide has been reported to inhibit H_2O_2-induced cataract formation *ex vivo* at concentrations of 0.1 to 10 mM (144), as well as selenite and l-buthionine-(S, R)-sulfoximine-induced cataracts *in vivo* at an intraperitoneal injection dose of 250 mg/kg/day (145,146).

3. Protein aggregation inhibitors

The human lens is primarily comprised of crystallins whose native tertiary structures and solubility ensure lens transparency (147). The crystallin superfamily includes α-, β- and γ-crystallins (148). During lens differentiation, crystallin levels are highly upregulated, while degradation of organelles such as nuclei, mitochondria, endoplasmic reticulum, and ribosomes occurs (148). Both gene mutation, which is considered to be related to congenital cataract, or age-related protein damage induced by UV radiation, oxidative stress and other factors such as hyperglycemia, may lead to the generation of light-scattering protein particles and cataract formation (18).

Furthermore, the mature fiber without organelles lacks the protein synthesis and degradation machinery necessary for removing and replacing damaged proteins (148). Therefore, the native conformations of crystallins must have superior solubility and long-term stability (147). If not, preventing or reversing protein aggregation is an important and novel strategy for cataract prevention and treatment.

Lanosterol and 25-hydroxycholesterol. In a landmark publication, Zhao *et al* (149) were the first to demonstrate *in vitro* that lanosterol reverses protein aggregation in cataracts in a concentration-dependent manner, from 0 to 40 μM. Lens-enriched lanosterol is the first sterol intermediate in the cholesterol biosynthetic pathway, which is mediated by lanosterol synthase (LSS) (149). Zhao *et al* (149) first identified that two mutations of the LSS gene, G588S and W581R, disrupted the cyclase activity of the LSS protein, resulting in congenital cataracts. Exogenous expression of wild-type LSS prevented intracellular protein aggregation, which was caused by various crystallin mutations. Furthermore, *in vitro* studies with dissected rabbit cataract lenses cultured with 25 mM lanosterol (dissolved in vehicle) and *in vivo* research with dogs administered intravitreal injections of 2 mg/ml lanosterol loaded nanoparticles every 3 days confirmed the effect of lanosterol in reducing cataract severity and increasing lens transparency by reversing protein aggregation (149). Consistently, in 2022, two reports confirmed the inhibitory effect of lanosterol on cataract lenses (150,151). First, Deguchi *et al* (151) designed ophthalmic nanosuspensions with 0.5% lanosterol and 0.6% nilvadipine to treat selenite-induced cataracts in rats for 28 days. The combined drugs were successfully delivered into the lenses of the rats. The treatment reduced the opacity levels in the cataracts of the rats by inhibiting the Ca^{2+} upregulation, which is related to selenite-induced nuclear cataract formation (151). This study provided a potential new treatment method for lens opacification in the future. Simultaneously, Zhang *et al* (150) used a subconjunctival drug release system to test nanoparticulated lanosterol on the cataract lenses of cynomolgus monkeys. The authors observed that, along with an increased lanosterol concentration in the aqueous humor, the cortical cataract severity was reduced. However, the drug had little effect on nuclear cataracts, which may be due to the lens nuclear barrier (152). Mechanistically, lanosterol administration increased the solubility of lens proteins and reduced oxidative stress by enhancing total antioxidant capacity and decreasing GSSG/GSH ratio in the lens cortex (150), and its effect was dependent on the severity of the condition or the lanosterol concentration in aqueous humor which varies from 0 to 31.61 ng/ml (150,153). Besides, LSS, the key enzyme for lanosterol synthesis, is also reported to protect lens epithelial cells against UVB-induced crystallin aggregation and oxidative stress (154), and to alleviate lens opacity in age-related cortical cataracts (155). Collectively, these investigations demonstrated that lanosterol prevents and reverses lens protein aggregation and also reduces oxidative stress, suggesting a novel strategy for the prevention and treatment of cataracts.

The analog of lanosterol, 25-hydroxycholesterol, has also been demonstrated to have a similar effect but a different mechanism in cataract prevention and therapy (156). Lanosterol can release all crystallin members by possibly binding with and destabilizing the intramolecular β-sheet structures of the crystallin aggregates (156). Specifically, Kang *et al* (157) showed that lanosterol binds to the hydrophobic dimerization interface to disrupt the aggregation of human γD-crystallin. However, 25-hydroxycholesterol distinctly dissociates α-crystallin via a certain binding site such as the dimer interface (158,159). Although 25-hydroxycholesterol is specific to α-crystallin, it is able to improve the transparency a solution composed of various crystallins. This may be due to the release of α-crystallin, which weakens the intermolecular interactions in the aggregates (156).

Although, lanosterol and 25-hydroxycholesterol have shown promising results in preventing and treating cataracts by dissolving lens crystallin proteins, certain researchers have doubted these effect. First, Daszynski *et al* (160) found that 0.2 mM lanosterol and 0.25 mM or 0.5 mM 25-hydroxycholesterol did not raise the soluble lens protein levels and restore cataract lens clarity. Second, the therapeutic effect of lanosterol has not been observed in some *in vivo* cases. For instance, it was reported that 25 mM lanosterol failed to reverse opacification of human senile cataract nuclei (161) and had little effect on the nuclear cataracts of cynomolgus monkeys (150). These findings indicate that the therapeutic potential of lanosterol may be restricted by its capacity to dissolve protein aggregates or by its concentration and the cataract type and severity. Therefore, further studies to elucidate the pharmacological mechanisms of lanosterol and 25-hydroxycholesterol are necessary to promote utilization in the clinical treatment of cataracts.

Mini-chaperones. In the vertebrate lens, crystallins (α-, β- and γ-) are typically considered structural proteins that constitute nearly 90% of the total lens protein (162). However, α-crystallins, which are composed of the two subunits αA- and αB-crystallin, but not β- or γ-crystallins, are also small heat-shock proteins that act as molecular chaperones and anti-apoptotic proteins to help maintain lens clarity (163). α-crystallins contribute to the protection from numerous eye diseases including cataracts, retinitis pigmentosa and macular degeneration (164-166). In eye lenses, α-crystallins form short-range contacts with other crystallin proteins to avoid protein misfolding and aggregation-induced light scattering (164). Mutations as well as aging related modification of α-crystallins that affect the structure, oligomerization and chaperone function, lead to decreased solubility and increased protein aggregation, making the lens prone to the development of congenital or senile cataracts (163). Thus, modulating chaperone activity by increasing the chaperone concentration in the lens is one important strategy to interfere with protein aggregation in the lens. Since the penetration to the eye is limited by the size, stability and post-modification of chaperones (162), the mini-chaperone peptide is a potential candidate molecule for therapeutic use in diseases associated with protein aggregation such as cataracts.

Previously, investigators established that both the mini-αA70-88 (KFVIFLDVKHFSPEDLTVK) and mini-αB73-92 (DRFSVNLDVKHFSPEELKVK) peptide chaperones have a similar effect on preventing protein aggregation of the native α-crystallin subunits (167,168). These mini-chaperones had already been demonstrated to inhibit selenite-induced cataract

Table I. Potential therapeutic use and mechanism of action of antioxidants in cataracts.

Potential therapeutic agents	Potential therapeutic use	Mechanism of action
Vitamin C	Prevention of ROS-, UVB- and STZ-induced cataracts; selenite-induced nuclear cataracts, age-related cataracts; may promote cataractogenesis	Antioxidant: Eliminate free radicals (34,35), prevents membrane lipid peroxidation and Na^+K^+-ATPase pump damage (28,39,40) and decrease γ-crystallin leakage (48) Pro-oxidant agent: Promote Fenton-reaction (51), enhance oxoaldehyde stress (56,57), cause glycation andcross-linking of crystallins (56,57). Its oxidation products exerts protein glycation and cross-linking (54,55).
Vitamin E	Senile cataract; hyperglycemia-, ionizing-, steroid-, UV-, selenite-induced cataract	Scavenge free radicals (62,63), increase GSH and GPx but decrease MDA levels (65).
Lutein	Senile cataract, UV-induced cataracts, diabetes-related cataracts, PCO	Neutralize free radicals (73,74), maintain GSHlevel (79), inhibit JNK and p38 activation (76),attenuates photo-induced oxidation of lens proteins (74), inhibitN^{ε}-(carboxymethyl) lysine and N^{ε}-(carboxyethyl) lysine generation (78).
EGCG	H_2O_2-and UVB-induced cataract, diabetic cataract, PCO	Scavenge free radicals (83), chelate metalions (83), activate MAPKs and Akt pathways (84), inhibit AIF/ EndoG pathway (85), suppress c-fos, c-myc, P53 expression (89) and inhibit protein aggregation:Inhibit αA,αB, γB-crystallin aggregation (87,88,90).
Resveratrol	Diabetic cataract, senile cataract, PCO	Neutralize free radicals (95), enhance catalase, SOD-1 and HO-1 expression, activate autophagy (96), reduce BAX/ Bcl-2expression of P16 and P21 and the ratio of (108) and activate Sirt1/Nrf2 signaling pathway (108).
Melatonin	H_2O_2- and UVB-induced cataracts; senile cataracts; diabetic cataracts	Activate GSH synthesis and scavenge free radicals (112), activate PI3K/Akt pathway (114), regulateSIRT6/p-Nrf2/ GPX4 and SIRT6/NCOA4/FTH1 pathways (115), decrease AR activity (118), increase SOD activity and decrease MDA levels (118,122).
Caffeine	UV-, selenite-, high sugar-and high fat-induced cataracts	Inhibit lipid peroxidation and scavenge hydroxyl radical (.OH), peroxyl radical (ROO.) and singlet oxygen ($^1O_2$) (127), retain GSH and ascorbic acid (128), suppress toxic miRs generation (125).
N-Acetylcarnosine	Senile cataracts and diabetic cataracts	Metabolize into L-carnosine (131), inhibit oxidation, glycation of proteins and attenuate protein cross-linkage and DNA damage (75,136,137) and reduce lens cell telomere shortening (75,136,137).
N-acetylcysteine	Diabetic cataracts, triamcinolone acetonide-, selenite-, hyperoxia- and H_2O_2-induced cataracts	Increase GSH generation and protect sulfhydryl groups from oxidation (139).

ROS, reactive oxygen species; STZ, streptozotocin; GSH, glutathione; MDA, malondialdehyde; PCO, posterior capsular opacification; SOD, superoxide dismutase; HO-1, heme oxygenase-1; NCOA4, Nuclear receptor coactivator 4; FTH1, ferritin heavy polypeptide 1; AR, aldose reductase; GPx, Glutathione Peroxidase; AIF, apoptosis-inducing factor; EndoG, Endonuclease G.

formation in rats by intraperitoneal injection at concentrations of 2.5-10 μg per animal (169). The prevention of cataract development by these mini-chaperones is achieved by inhibiting stress-induced apoptosis as well as protein aggregation (169). It has been suggested that these mini-chaperones provided Bax and procaspase-3 binding sites to inhibit their activities and inhibited cytochrome c release (169). However, the mechanism by which these mini-chaperones interact with their substrate proteins to inhibit protein aggregation has not yet been elucidated (169). Furthermore, the αA-mini-chaperone has also been shown to stabilize the cataract causing αA-crystallin mutant, αAG98R, and rescue its chaperone activity (170).

Table II Potential therapeutic use and mechanism of action of protein aggregation inhibitors in cataracts.

Potential therapeutic agents	Potential therapeutic use	Mechanism of action
Lanosterol	Cortical cataract, congenital cataract, and selenite-, UV-induced cataracts	Increase solubility of lens proteins by binding with all crystallins (149-151), reduce oxidative stress (150,154,155).
25-hydroxycholesterol	Cortical cataracts	Specifically dissociate α-crystallin and weakens the intermolecular interactions (156,158,159).
Mini-chaperones	Congenital cataract, oxidative stress-induced cataracts	Act as chaperones to interact with their client proteins (167,168), provide Bax and pro-caspase-3 binding sites to inhibit their activity and inhibit cytochrome c release (169), stabilize mutant αAG98R and rescue its chaperone activity (170) and anti-apoptotic property similar to the native crystallin (169).
Rosmarinic acid	Age-related cataract, estrogen deficiency- and selenite-induced cataracts	Reduce cataract microparticle size and modify their amyloid features (173) and inhibit oxidative stress (174,175).

The covalent interactions of the αA-mini-chaperone with the αAG98R subunits has been detected (170). γD-crystallin is the natural substrate of αA-crystallin (171). A study by Banerjee *et al* (172) revealed that the αA-mini-chaperone binds to Phe56, Val132, and Val164 to Leu167 of γD-crystallin to protect it from aggregation and oxidation. In summary, mini-chaperones that exhibit a specific binding affinity for crystallin and anti-apoptotic properties serve as promising drug candidates for cataract prevention and treatment.

Rosmarinic acid. Besides sterols, a phenolic compound, rosmarinic acid has also been identified as a lenticular protein aggregation inhibitor (173), as well as an antioxidant (174,175). In 2018, Chemerovski-Glikman *et al* (173) reported that they had developed an *ex vivo* screening platform in which human lens particles removed from patients during cataract surgery were treated with different protein aggregation modulator candidates. The study confirmed the efficacy of 25-hydroxycholesterol in reducing the cataract protein load. Moreover, it was revealed that rosmarinic acid was potent cataract modulators and exhibited improved optical clearance abilities compared with sterols. Furthermore, an *in vivo* study in which model rats were subcutaneously injected with rosmarinic acid confirmed that it ameliorated cataract formation by modulating protein aggregation (173). Mechanistically, rosmarinic acid reduces cataract microparticle size and modifies their amyloid-like features (173). Additionally, as an antioxidant, intraperitoneally injected rosmarinic acid reduces estrogen deficiency- and selenite-induced cataract development by inhibiting oxidative stress (174,175).

4. Discussion

Cataract is a major ophthalmic disease causing severe visual impairment and even blindness in patients (1,2). To date, cataract surgery is still the only effective treatment method (3). However, cataract surgery has a number of limitations. Surgery has a great economic burden on public health and patients, and some patients may not even be able to have surgery due to a lack of access and resources (4-6). Additionally, surgery may cause PCO and further vision loss (7). Therefore, researchers are continuously seeking an available and effective non-surgical method to prevent and treat cataracts.

Cataract development has several unknown causes; however, oxidative stress is known to cause and develop cataracts (20,106,130,143,174). The disturbance of pro- and antioxidant systems leads to hyper-levels of free radicals, which attack other molecules, thus resulting in aging-related diseases such as glaucoma and cataracts (29). Therefore, inhibiting pro-oxidants or enhancing the levels of antioxidants are primary strategies to prevent cataracts. Vitamins, carotenoids, polyphenols, melatonin, caffeine, *N*-acetylcarnosine and *N*-acetylcysteine are strong antioxidants that target oxidative stress in the pathogenesis of cataracts (19,28,107,118,132,145,176). These antioxidants have been demonstrated to prevent or slow the progression of cataracts *in vitro*, *ex vivo* and *in vivo* (31,106,116, 130,143,144). Carotenoids and polyphenols inhibit cell fibrosis and EMT, suggesting secondary cataract PCO prevention potential (81,109). Besides their antioxidative and anti-cataract properties, certain antioxidants (such as vitamins) also display lens toxicity, which may be related to hyper-dosage or oxidizing metabolites (56). Moreover, some antioxidants (such as EGCG and *N*-acetylcysteine) inhibit protein aggregation, thus enhanced their application prospects in cataract prevention and treatment (87,138) (Table I). However, only N-acetylcarnosine has experimentally demonstrated a partial efficacy in the restoration of vision (30). Consequently, further research is warranted to devise a comprehensive strategy that enhances both the prophylactic efficacy of antioxidants and

combines the therapeutic efficacy of other pharmacological treatments in cataract.

Crystallins are the vital structural and functional proteins that are responsible for the refractive index in the lens (177). The structural conformational changes caused by post-translational modifications or mutations produce a disorder of crystallin-crystallin interactions and lenticular opacity (18,163). Inhibiting or reversing crystallin aggregation is another major effective strategy for cataract prevention and treatment (90,156). Zhao *et al* (149) first revealed that lanosterol reverses protein aggregation in cataracts. Lanosterol releases all crystallin family members, while its analog, 25-hydroxycholesterol, specifically dissociates α-crystallin (156). With different mechanisms, these drugs display similar crystallin aggregation inhibition effects (149,156,173). Although they are promising anti-cataract drugs, these drugs have little effect on nuclear cataracts, suggesting multiple variables restrict their therapeutic effect (150,161), such as the lens nuclear barrier (150).

In the lens, high levels of chaperone protein are vital for transparency maintenance (158,164). Due to gene mutation, oxidative stress or environmental factors, these proteins may lose their chaperone activity and become part of aggregates forming the cataract (163). Thus, increasing the activity or concentration of these chaperones in the lens would be an effective strategy for cataract treatment. Recently, mini-chaperones have been found to act like the native proteins, inhibiting oxidative stress and protein aggregation (162,169). Further study is imperative to promote its translation from bench to the clinic. Recently, the phenolic compound, rosmarinic acid, has also been proposed to be an anti-cataract candidate as it has lenticular protein aggregation and antioxidative properties (173) (Table II).

Considering the blood-ocular barrier as well as the lens nuclear barrier (152), an appropriate drug delivery system is also a vital subject for lens drug research. Eye drops, suspensions or ointments are the primary forms with very low levels of bioavailability (178,179). Nanoparticles and nanosuspensions can be used to increase drug delivery and bioavailability (178,179). Moreover, researchers have improved lens opacity with an anti-cataract drug-containing nano system (108,151,153). Thus, comprehensive consideration of pharmaceutical preparations is beneficial to promote clinical anti-cataract drug research.

Cataract caused one fifth of visual problems worldwide (180), unfortunately, there is no well-established and approved non-surgical strategy developed for cataract treatment (3). Considering the biochemistry of cataract formation, the primary strategies for its prevention and treatment involve the inhibition of apoptosis and protein aggregation. However, both approaches exhibit significant limitations. Most antioxidants are capable of attenuating reactive oxygen species (ROS)-induced apoptosis but demonstrate minimal efficacy in cataract treatment. Conversely, protein aggregation inhibitors, while able to inhibit or reverse protein aggregation, show limited effectiveness in cell apoptosis inhibition as well as preventing and reversing cataracts. Therefore, the development of a nanosystem that incorporates both antioxidants and protein aggregation inhibitors may enhance the overall effectiveness of cataract prevention and treatment.

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Authors' contributions

LW, XLi, JL wrote and revised the main manuscript, XM and XLiu collected and analyzed the data. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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