Review Article

Recent Advances and the Mechanism of Astaxanthin in Ophthalmological Diseases

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Astaxanthin (AST) is a naturally occurring carotenoid that has strong antioxidant, anti-inflammatory, and antiapoptosis effects and is used for the prevention of cancer. There is growing evidence that AST has multiple protective effects against various eye diseases. This article reviews the function and the potential mechanism of AST in dry eye syndrome, keratitis, cataract, diabetic retinopathy, age-related macular degeneration, high intraocular pressure, and other ocular diseases. It provides a theoretical basis for the clinical application of AST as a potential nutraceutical.

1. Introduction

Astaxanthin (AST) is a lipid-soluble and red-orange carotenoid pigment that belongs to a group of carotenoids called xanthophylls [1, 2]. In 1938, Kuhn et al. originally discovered AST in lobsters as a source of pigment in aquaculture. It was found in various microorganisms and marine organisms, such as yeast, microalgae, salmon, and krill, as well as plants, such as the leaves, flowers, fruits, and feathers, playing a role mainly in color rendering [3–5]. In 1991, AST was approved as a food supplement, and its biological activity, antioxidant properties, and physiological properties as a precursor to vitamin A were reported in rats and fish [6]. The chemical name of AST is 3,3′-dihydroxy-4,4′-diketo-beta, beta′-carotene [7]. It has an extended structure with a polar region at both ends of the ion ring, which gives it the ability to neutralize free radicals. There is also a nonpolar zone in the middle, consisting of a series of carbon-carbon double bonds called "conjugation." Compared with 11 β-carotene, AST with 13 conjugated double polyunsaturated bonds has unique chemical properties, molecular structure, and light absorption properties [8]. The hydroxyl group at the 3,3′β position and the ketone portion of each ionone ring make the AST molecule more polar,

greatly enhancing its membrane function. The polar-non-polar-polar structure of the AST molecule allows it to precisely match the polar-nonpolar-polar regions of the cell membrane [9]. In comparison to other carotenes, AST has several common physiological and metabolic activities.

Due to the specific biological structure, AST can play an important role in a variety of biological processes, such as antioxidant, anti-inflammatory, antiapoptotic, and anticancer processes; it has a series of biological functions, such as protecting the cardiovascular system, delaying diabetic nephropathy and liver injury, having antiobesity properties, and improving immunity [10]. Currently, AST has become a hot research topic, and several recent studies have highlighted the potential protective role of AST in eye diseases. Although AST is not present in the retina, such as lutein and zeaxanthin, it can selectively cross the BRB and protect the retinal cells from oxidative damage [11]. Moreover, the prognosis of various eye diseases has significantly improved, including that of ocular surface diseases (dry eye and keratitis), fundus diseases (diabetic retinopathy, age-related macular degeneration, and ischemia), cataracts, and optic nerve-related diseases [11–17].

In our review, we systematically summarized and highlighted the protective effects of AST on eye diseases. The

effects of AST on ocular tissue cells and its molecular mechanisms involved, such as the regulation of antioxidant and antioxidant activation, the regulation of immune response, the prevention of cell damage, and the regulation of apoptosis, were discussed further. This review article discussed the therapeutic potentials and health benefits of AST in ocular disease.

2. Main Biological Activities of AST

2.1. Antioxidant Activity. Oxidative stress is caused by the imbalance of oxidation or the antioxidant reaction in cells, which promotes the production of excessive reactive oxygen species and free radicals [18]. Excessive oxidative factors are an important mediator in the pathological process of diseases. They may react with proteins, lipids, and DNA through chain reaction to induce protein inactivation, lipid oxidation, and DNA damage, causing many diseases [19]. The structure of AST determines its strong antioxidant ability. The polyene chain can capture free radicals in the cell membrane, and the terminal ring can scavenge free radicals inside and outside the cell membrane [20]. Therefore, AST protects the membrane structure by neutralizing singlet oxygen, preventing chain reactions, and inhibiting lipid peroxidation (LPO), hence, increasing the function of the antioxidant enzymes [21, 22]. AST can increase the levels of antioxidants catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in the hippocampus of type 2 diabetic rats, therefore, increasing the antioxidant capacity of the hippocampus [23]. In addition, another survey showed that AST can significantly increase the activity of GPx and SOD, protecting mouse hepatocytes from oxidative damage by using hydrogen peroxide [24]. Fakhri et al. also found that AST can increase the expression of glutathione S-transferase $\alpha 1$ (GST-$\alpha 1$), which enhances the biological defense against oxidative stress damage via the activation of the extracellular signal-regulated protein kinase (ERK) signaling pathway in vitro and in vivo [10].

2.2. Anti-Inflammatory Activity. Inflammation is a complex series of immune responses, which act as a host defense mechanism or a response to body damage when initiating tissue repair process [25]. However, excessive or uncontrolled inflammation is harmful to the host and may cause damage to the host cells and tissues [26]. AST is a strong antioxidant, which can prevent inflammation of the biological system. It plays an important role in preventing the progression of central nervous system diseases and protecting both acute and chronic organs (lung, kidney, and liver) inflammatory injury. Further researches showed that AST blocks the nuclear factor kappa-B (NF-κB) dependent signaling pathway; it also forestalls gene expression of downstream inflammatory mediators, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [22, 27–29]. It suppresses the levels of inflammatory factors (TNF-α and IL-6) through the inhibition of mitogen activated protein kinase (MAPK) and nuclear factor-activated pathways, which prevents acute lung injury

[30]. In addition, AST can reduce the expression of interleukin-8 in infected gastric epithelial cells [31]. Moreover, Han et al. found that AST prevents ethanol-induced hepatic injury via directly binding to the DNA binding site of STAT3 and inhibiting its activity; this reduces inflammatory responses [32].

2.3. Antiapoptosis Activity. Recent studies have shown that apoptosis is associated with many diseases, such as autoimmune diseases, neurodegenerative diseases, tumors, AIDS, and multiple organ dysfunction syndrome [33–36]. AST can modify some key apoptotic proteins to prevent the occurrence of related diseases [37]. Kowshik et al. reported that AST can promote cell apoptosis in oral squamous cell carcinoma models, and it plays a role as a tumor suppressor by downregulating noncoding RNAs, miR-21, and HOTAIR via the PI3K/Akt pathway [38]. AST can induce antiapoptosis activity in the classic mitochondrial pathway, which is closely related to reactive oxygen species (ROS), Bax, Bcl-2, P53, and other molecules. For example, AST can protect renal tubular epithelial cells from acute injury by downregulating proapoptotic proteins, P53 and Bax, and upregulating the expression of antiapoptotic protein Bcl-2 [39]. Naguib reported a greater antioxidant activity in AST in comparison to different carotenoids, such as α-carotene, lycopene, lutein, and β-carotene [40]. In vivo and in vitro studies on rats have shown that AST affects immunity; however, no clinical research has been conducted on humans [21, 41].

3. Ocular Diseases

3.1. Clinical Study. Preclinical and clinical evidence supports the potential use of AST in the prevention and treatment of a number of ocular diseases. The existing clinical research relating to AST primarily focuses on dry eye syndrome (DES), and age-related macular degeneration (ARMD) [14, 42, 43] (Table 1).

DES is a disorder of tear deficiency or excessive tear evaporation, resulting in an unstable tear film [46]. In a prospective, single-center, one-group, quasiexperimental study, a supplement of 6 mg AST twice a day improved the symptoms and signs of patients with mild-to-moderate DES [42]. The index, such as ocular surface disease index (OSDI) questionnaire score, noninvasive tear break-up time (NIBUT), fluorescein break-up time (FBUT), corneal fluorescein staining (CFS) score, eyelid margin signs, meibomian gland (MG) expressibility, meibum quality, and blink frequency improved significantly to varying degrees after treatment compared with those before the treatment [42]. Furthermore, a prospective, randomized, double-blinded study demonstrated that oral AST supplementation may increase tear production and improve tear film stability by reducing levels of ROS [14]. Further large and long-term studies are needed to determine the benefits of oral AST supplementation in patients with DES.

Age-related macular degeneration (ARMD) is the leading cause of visual impairment and blindness in some

TABLE 1: Summary of in clinical studies on eye and AST.

Study type	Number	AST dose and duration	Referred ocular disease	Biological effects	Index	References
Prospective, One-group	60 patients/ 120 eyes	12 mg/day 30 ± 2 days	DES	Improve the symptoms and signs	Osd, tbut, FBUT, CFS, MG	[42]
RCT	43	20 mg/kg/day 8 weeks	DES	Improve tear production and tear film stability Reduce levels of ROS	Schirmer test, TBUT	[14]
RCT	20	12 mg/day 4 weeks	ARMD	Choroidal blood flow velocity	—	[44]
RCT	27	4 mg/day 12 months	ARMD	—	mfERG	[43]
RCT	145	4 mg/day 12 months	ARMD	Stable/improve contrast sensitivity and visual acuity	—	[45]
RCT	35	6 mg/day 2 weeks	ARMD	Affect O2.- scavenging activity in the aqueous humor	—	[1, 49]

developing countries and developed countries among people aged over sixty-five years. ARMD is characterized by retinal pigment epithelium (RPE) cells within the damaged macula, leading to foveal photoreceptors loss [47]. AST intake leads to prevention and inhibition of dry ARMD progression [48]. A randomized controlled trial (RCT) reported that supplementation with carotenoids and antioxidants (including vitamin C (180 mg), lutein (10 mg), zeaxanthin (1 mg), and AST (4 mg) selectively improved central retinal dysfunctions (0°–5°). However, no functional changes were present in the more peripheral (5°–20°) retinal areas [43]. Another two-year RCT study demonstrates that oral lutein/zeaxanthin combined with additional carotenoids (AST) can clinically improve and stabilize visual acuity, contrast sensitivity, and visual function in ARMD patients [44]. However, carotenoid mixtures including AST were used in the above studies, and there has been no direct study that shows the effectiveness of AST clinically.

Three clinical studies were conducted to explore the mechanism of AST in protecting visual functions [1, 49, 50]. AST intake may have affected vascular endothelial growth factor (VEGF) levels in the aqueous humor through its antioxidant effects by increasing O_2^- scavenging activity and suppressing peroxide production [1]. Moreover, these previous studies reported that the effects of AST on VEGF level and antioxidative activities differed by sex. The VEGF level in the female aqueous humor was regulated by the overall extent of oxidation. Furthermore, AST affected O_2^- scavenging and participated in the regulation of VEGF level in the female aqueous humor [49]. Saito et al. confirmed that AST increased the choroidal blood flow velocity in the macular region, improved the local blood circulation in the eyes, and improved the ocular circulation. It was a randomized, double-blind, placebo-controlled trial where 20 normal subjects took 12 mg AST a day for four weeks [50]. This study has shown that AST significantly increased the choroidal blood flow with no side-effects; however, it is still unknown as to whether this effect is temporary or permanent [50].

3.2. In Vivo Animal Study. Numerous animal studies have further confirmed the protective effects of AST on the eye and its effectiveness in the prevention of ocular diseases, ranging from the ocular surface to the fundus, including DES, phototoxic keratitis [44], cataract [51], diabetic retinopathy [11], ARMD [48, 52], retinal ischemia injury [53], and other ocular diseases. All the details are presented in Table 2.

Under normal circumstances, the cornea absorbs most of the UV-B and UV-C radiation and protects the inner eye against UV-induced damaging effects. Exceeding the threshold levels of UV-B can induce inflammation of the cornea; this is called photokeratitis, which appears 6 to 12 hours after exposure [61]. The mechanisms involved include oxidative stress, DNA damage, and death receptor activation, all of which lead to apoptotic cell death [62]. Recently, Lennikov et al. reported that the topical administration of AST provided successful prevention against UV-induced photokeratitis in mice. AST protected the corneal epithelium in a dose-dependent manner by inhibiting ROS production and NF-κB expression, further inhibiting inflammation. The anti-inflammatory activity of AST may be related to its antioxidant activity. In addition, they found that AST can suppress phototoxicity in the cultured mouse corneal epithelial cells (TKE2) in a dose-dependent manner. It prevents apoptosis of TKE2 cells by inhibiting NF-κB activation and reducing oxidative stress. This suggests that AST might be a candidate treatment against the deleterious effects of UV exposure, with better clinical benefits as compared to other molecules [44]. Harada et al. produced similar results. AST protects corneal epithelium cells by decreasing the level of ROS and inhibiting NF-κB activation and caspase-3-induced apoptosis. Inflammation was reduced by reducing the expression of cyclooxygenase-2 (COX-2), TNF-α, and CD45 in the corneal tissue [13]. Protective effects of AST on UV keratitis have not been proved in humans and further studies are needed.

Cataract is the leading cause of blindness and is an important cause of low vision globally [63]. The mechanism

TABLE 2: Summary of in vivo animal studies on eye and AST.

Study type	Animals	AST dose	Referred ocular disease	Biological effects	Related genes	References
In vivo	C57BL/6J mice	1/0.1/0.01 ng/ml by eye drop	Phototoxic keratitis	Increase corneal thickness, antiapoptosis, reduce ROS and NF-κB	NF-κB	[44]
In vivo	C57BL/6J mice	6 mg	Phototoxic keratitis	Improve corneal epithelial thickness Antiapoptosis Inhibit activity of NF-κB Decrease proinflammatory factors and ROS	NF-κB , caspase-3, CD45, COX-2, TNF-α,IκB	[13]
In vivo	Chicken embryo model	50/80/100 mg/ml	Cataract	Inhibit HC-induced cataract Reduced GSH levels	—	[54]
In vivo	Sprague Dawley rat	16/80 mg/kg	Cataract	Delay progress of cataract Protect epithelium of lens Decrease antioxidant levels	AGEs, SOD, GSH, CAT, MDA	[51]
In vivo	Db/db rats	25/5 mg/kg by oral gavage	Type 2 diabetes mellitus	Decrease levels of oxidative stress marker Inhibit apoptosis	MDA, 8-OHdG, SOD	[16]
In vivo	Psammomys obesus	10 mg/kg	Type 2 diabetes mellitus	Increase HO-1 expression Attenuates glial dysfunction	HO-1, glial markers (GFAP, CRALBP, and GS)	[55]
In vivo	Wistar rats	0.6/3 mg/kg	Type 1 diabetes mellitus	Decrease oxidative stress and inflammatory mediators and inhibit activity of NF-κB Increase antioxidant enzyme	8-OHdG, NO, acrolein, ICAM-1, MCP-1	[56]
In vivo	ddY mice	100 mg/kg	Retina ischemia (AMD, DR, glaucoma	Protect retinal functional and histological damage Decrease RGCs death	—	[53]
In vivo	C57BL/6J mice	10/100 ng/μL	Pathological retinal angiogenesis	Antiproliferation and antiapoptosis of endothelial cells Suppress CNV and macrophage infiltration	—	[57]
In vivo	C57BL/6J mice	1/10/100 mg/kg	AMD	Decrease expression of inflammatory and angiogenic molecules Inhibit activity of NF-κB	ICAM-1, MCP-1, IL-6, VEGF, VEGFR-1, VEGFR-2, IκB	[15]
In vivo	ddY mice	100 mg/kg	AMD/RP	Increase GCL and INL Inhibit oxidative DNA damage and lipid peroxidation damage Antiapoptosis	8-OHdG, 4-HNE	[58]
In vivo	ddY mice	100 mg/kg	AMD/RP	Ameliorate retinal dysfunction and histological damage Antiapoptosis	8-OHdG, ROS	[48]
In vivo	Glast ± mice and C57BL/6J mice	10/30/60 mg/kg	Normal intraocular glaucoma (NTG)	Suppress RGCs loss	4-HNE, pIκB, IκB	[59]
In vivo	C57BL/6J mice	50 mg/kg	Glaucoma	Protect retinal tissues and RGCs from oxidative stress Inhibit apoptosis of RGCs Active nrf2/HO-1 pathway	Bax, Bcl-2, Nrf2. HO-1, ROS	[11]
In vivo	Sprague Dawley rat	25/75 mg/kg	Retinal toxicity	Prevent retinal toxicity by CIS	GSH, MDA	[60]

of cataract development is not clearly defined. It is a multifactorial disease, and oxidative stress might be the leading cause. Oxidative damage to lens proteins is a major factor in cataract formation [64]. Under the action of external harmful or deleterious factors (ultraviolet radiation, drugs, changes in self-metabolic state), excessive free radical production and impaired antioxidant defense system causes lens epithelial cell apoptosis, lens protein aggregation, increased

ratio of insoluble protein to soluble protein, and impaired barrier function of the lens capsule [65]. These changes promote the occurrence and development of cataracts. Our study revealed that AST decreased the levels of glutathione (GSH), SOD, and CAT and increased the levels of malondialdehyde (MDA) and advanced glycation end products (AGEs) in the lens of rats with type I DM. AST also ameliorated the impaired morphologic changes and imparted a

TABLE 3: Summary of in vitro studies on eye and AST.

Study type	Cell lines	AST dose	Referred ocular disease	Biological effects	Related genes	References
In vitre	ARPE-19	0/5/10/20 μm	AMD	Attenuated H2O2-induced oxidative stress Active Nrf2-ARE, PI3K/Akt pathway	NQO1, HO-1, GCLC, GCLM, Nrf2, PI3K, Akt, caspase 3	[87]
In vitro	ARPE-19	50/150 μm	AMD	Inhibit inflammatory and angiogenic molecules and NF-κB activation	IL-6, VEGR-1, VEGR-2, MCP-1, ICAM-2, IκB, NF-κB, p65	[15]
In vitro	661W cells	3/10/20 μm	AMD	Active Nrf2 Reduce ROS production Mitigate photoreceptor cell death Reduce ROS production	Nrf2, c-Jun, phaseII enzymes (HO-1, Mqo-1, GCLM)	[52]
In vitro	661W cells	0–50 μm	AMD	Inhibit cell death, oxidative stress markers, phaseII enzymes expression and Nrf2/PI3K/Akt pathway	Bcl-2, Bax, PI3K, Akt, ROS phaseII enzymes (HO-1, NQO1)	[83]
In vitro	RGC-5	0.01/0.1/1/10 μm	Glaucoma	Reduce cell death and ROS production	—	[58]
In vitro	RGC-5	1/10/100 nm	Glaucoma	Increase survival rate of cell death induced by glutamate/oxidative stress/hypoxia Inhibit DNA oxidative damage, apoptosis and necrotic RGCs death	—	[84]
In vitro	RGC-5	0.1–10 μm	Retinal ischemia reperfusion	Reduced ROS production	—	[53]
In vitro	HCECs	0.2/1/2/10 μm	Phototoxic keratitis	Increase cell viability Reduced ROS production and age-related factors	ROS, p53, p32, p16	[85]
In vitro	HCECs TKE2 cells	1/0.1/0.01 mg/ml	Phototoxic keratitis	Decrease cytotoxicity	8-OHdG	[44]
In vitro	HLECs SRA 01–04	1/2/4 μm	cataract	Inhibit UV-induced oxidative stress activity and lipid peroxidation	p-JNK, p38	[86]

protective effect on diabetic cataracts [51]. The beneficial effect of AST on cataracts was also investigated in other experimental animal models. It was demonstrated that treatment with AST reduced lens opacity and prevented the development and progression of steroid-induced cataracts in chick embryo models. The researchers also showed that AST reduced glutathione levels in the lens [54]. It is recommended to do further research about the mechanism of AST as treatment for cataracts.

As mentioned above, the effect of AST on AMD has been widely studied in clinical research. The pathogenesis has also been further studied. An in vivo animal study considered the effect of AST on photoreceptor cell damage caused by light and pathological retinal angiogenesis. With age, cumulative photodamage and retinal susceptibility lead to ROS accumulation and a significant decrease in enzymes, such as SOD, CAT, and GPx [66]. Tomohiro et al. reported that AST protected the photoreceptor cells at a dose of 100 mg/kg and inhibited retinal dysfunction in terms of electroretinogram (ERG) and outer nuclear layer (ONL) loss and reduced the expression of apoptotic and 8-OHdG-positive cells, induced by light exposure via its antioxidative effect mechanism. Moreover, AST protected against increases of PI-positive cells and intracellular ROS activity in retinal core cells [48, 52]. Pathological neovascularization of the retina is another important cause of choroidal neovascularization (CNV) and AMD [57]. Otsuka et al. found the possibility of AST supplementation as a therapeutic strategy in

suppressing CNV-associated ARMD in C57BL/6J mice [15]. AST can also downregulate the expression of VEGF, which can be used as a potential nutritional drug to prevent or treat retinal dysfunction in diabetic patients. AST can block the activation and translocation of HIF1α and XBP1 induced by high glucose or CoCl and downregulate the expression of HIF1α and XBP1. In addition, AST protected the disintegration of occlusion zone-1 (ZO-1) tight junction proteins in RPE and reduced the permeability of RPE cells induced by Mercury or hypoxia [11]. In addition, intravitreal and intraperitoneal AST administration can both inhibit retinal endothelial cell proliferation and exert an antiangiogenic effect. AST also offers a dose-independent reduction in mitochondrial injuries and a dose-dependent inhibition of apoptosis in a HIR newborn mouse model. The most effective route seems to be intravitreal high-dose AST injection [57]. In conclusion, AST can protect the RPE layer from oxidative damage and prevent CNV formation, thus, delaying the occurrence and development of ARMD. These results may provide great advancements in the treatment of such disease.

Diabetic retinopathy (DR) is one of the important and common microvascular complications of diabetes mellitus (DM) [67]. It is reported as one of the major causes of blindness and visual impairment in adults [68]. Oxidative stress and inflammation are the two determinant factors in the initiation and progression of DR [69]. High oxygen consumption makes the retina more vulnerable to oxidative
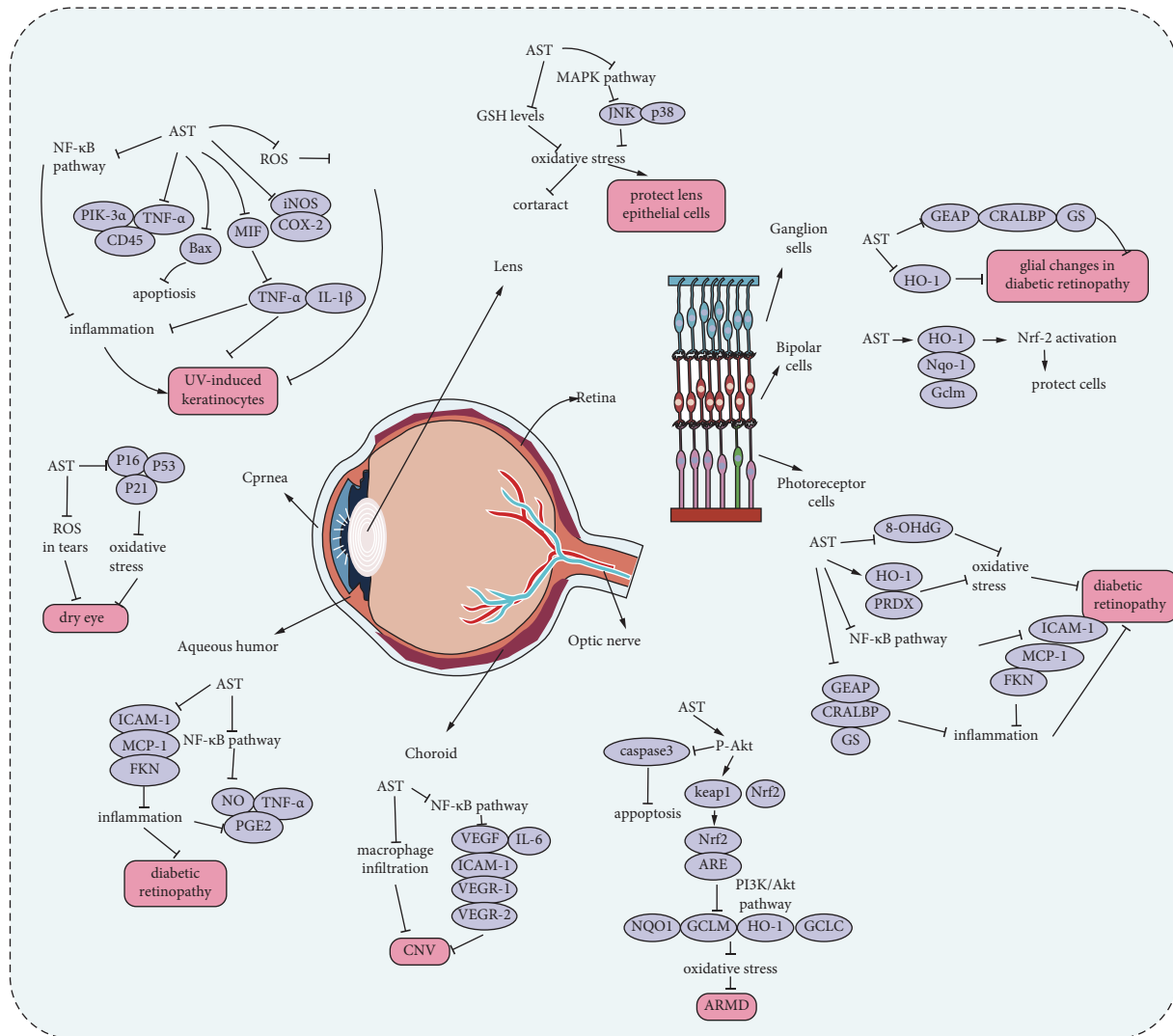
Figure 1: An illustration of AST targets in the ocular diseases.

stress. Thus, ROS induced apoptosis in retinal ganglion cells or photoreceptor cells plays an important role in DR. This increases the release of inflammatory cytokines thru the activation of NF-κB [70, 71]. Yeh reported that AST significantly reduces the levels of oxidative stress mediators (8-OHdG) and inflammatory mediators, such as intercellular cell adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and fractalkine (FKN). Moreover, AST also increases the levels of antioxidant defense enzymes, such as HO-1, and inhibits NF-κB activity, which promotes the release of inflammatory mediators, indicating that AST may be a beneficial nutritional supplement to halt the progression of DR and prevent vision loss in patients with diabetes in the retinas of streptozotocin-induced diabetic rats [56]. Similarly, Baccouche et al. found that short-term treatment of AST attenuated glial dysfunction and promoted the expression of oxidative stress marker HO-1, reducing glial reactivity in the diabetic retina of rats and exhibiting a protective effect [55]. However, the short-time administration of AST did not rescue the

expression of the retinal ganglion cell marker, Brn3a, and synaptophysin, a marker of presynaptic vesicles [55]. AST improved oscillatory potentials (OPs) and decreased apoptosis of retinal ganglion cells (RGCs) and inhibited the increase of MDA and 8-OHdG levels; it showed an anti-oxidative effect in the retina of db/db mice [16].

Retinal ischemia is a common clinical condition that often leads to visual impairment and blindness [72]. Ischemia in the retina and optic nerve is involved in the pathogenesis of major retinal diseases, such as ARMD, DR, and glaucoma. Ischemia induces the release of neurotransmitters, which causes membrane depolarization, increase in intracellular calcium concentration, and production of nitric oxide (NO) and ROS [73, 74]. When ROS, such as superoxide anion radicals, their dismutation product H_2O_2, and hydroxyl radicals are overproduced, they induce cell death [75]. In the present study, oral administration of AST at 100 mg/kg significantly prevented ischemic retinal cell damage [76]. Otsuka et al. demonstrated the protective effects of AST against retinal histological

damage after ischemia or reperfusion injury. AST increases the number of RGC and the thickness of inner plexiform layer (IPL) and inner nuclear layer (INL) by reducing ROS production [53]. Oral administration of AST might be effective in protecting against neurodegeneration during ischemic retinopathy.

Glaucoma is a chronic neurodegenerative disease characterized by high intraocular pressure, which is the main cause of blindness worldwide [77]. It can lead to apoptosis of RGCs and gradual loss of optic nerve axons, further causing visual field defects in glaucoma patients [78]. AST reduced retinal oxidative stress injury by activating the Nrf2/HO-1 pathway, thereby inhibiting RGC apoptosis and protecting the integrity of the retinal structure. Moreover, Li et al. reported that AST can significantly alleviate the symptoms of patients during adjuvant treatment for acute glaucoma [79]. Cort et al. also found that AST had a protective effect on the retinas in rats with elevated intraocular pressure (EIOP). The amplitude of visual evoked potential (VEP) P100 in the experimental group returned to control levels after AST treatment. AST had an inhibitory effect on apoptosis of RGCs, demonstrating the protective effect of AST in glaucoma and other optic neuropathies [12]. AST exerts antioxidative stress and neuroprotective effects on inhibiting RGC degeneration and retinal degeneration in a mouse model of NTG, indicating that AST may be a potential therapeutic agent for the treatment of glaucoma [59].

Few studies have assessed retinal drug toxicity induced by antitumor drugs and uveitis [60, 80]. Cisplatin (CIS) is widely used to treat various cancer types, such as head, neck, ovarian, testicular, breast, and small lung cell [80–82]. However, as a rare condition, its retinal toxicity is stated in a few case reports and its mechanism is still unclear [60, 81]. Fındık et al. found that AST treatment reduced the increase in MDA, eNOS, and 8-OHdG levels and increased the levels of GSH expressions in the retinas of rats following CIS administration [60]. However, the antitumor effect of CIS was explained by DNA adduct formation, ROS accumulation, lipid peroxidation, and mitochondrial stress increase. Hence, further studies are necessary to define the optimal doses of AST for protecting the retinal tissues without sacrificing the main purpose of CIS therapy in the future [60]. With regard to the uvea, there are only a few studies on the effect of AST on uveitis. Studies have shown that AST can significantly decrease the number of infiltrating cells in the anterior chamber and the concentration of protein, NO, TNF-α, and prostaglandin E2 (PGE2) in the aqueous humor in rats with endotoxin-induced uveitis (EIU). The number of activated NF-κB-positive cells was lower in the iris-ciliary bodies, which suggests that AST reduces ocular inflammation in the eyes with EIU by downregulating proinflammatory factors and by inhibiting the NF-κB-dependent signaling pathway [80]. AST also has an anti-inflammatory effect on the choroid.

3.3. In Vitro Study.
In studies that investigated the effect of AST on ocular diseases, the common cell models included RPE cells [15], photoreceptor cells [83], retinal ganglion cells (RGCs) [84], corneal epithelium cells [85], and lens epithelial cells [86], which correspond to one or more ocular diseases and elaborate relevant mechanisms (Table 3). The effect of AST on RPE is currently the most researched in in vitro studies. Li et al. found that AST clearly reduced H2O2-induced ARPE-19 cell viability loss, cell apoptosis, and intracellular generation of ROS via Nrf2-mediated upregulation of the expression of phase II enzymes, involving the PI3K/Akt pathway [88]. In addition, Izumi et al. found that AST could inhibit the expression of inflammation-related molecules and angiogenic molecules, including VEGF, IL-6, ICAM-1, MCP-1, and vascular endothelial growth factor (VEGFR-1 and VEGFR-2). Furthermore, AST suppressed the activation of the NF-κB pathway, including NF-κB degradation and p65 nuclear translocation. They also suggested that AST had an early intervention effect on CNV [15].

AST mainly exerts antioxidative and antiapoptotic functions in photoreceptor cells. Recent studies have reported that AST can protect against light-induced injury of the photoreceptor cells by activating nuclear factor 2 (Nrf-2) and by reducing ROS production [52]. Nrf2 is a transcription factor that regulates the antioxidant responses via modulating the expression of phase II enzymes expression such as heme oxygenase-1 (HO-1), NAD (P) H: quinone oxidoreductase (NQO-1), and g-glutamyl-cysteine ligase (GCL) [83]. Lin et al. reached a similar conclusion that AST inhibited the blue light-emitting diode-induced apoptosis, ROS production, expression of oxidative stress biomarkers (8-OHdG, nitrotyrosine, and acrolein), and mitochondrial damage in an LED-induced retinal injury cell model by free radical scavenging activity, inducing phase II antioxidant enzyme expression, and activating the PI3K/Akt/Nrf2 pathway [83]. Light can also cause corneal epithelial damage, and AST has a certain protective effect on the lens due to its strong antioxidant capacity, preventing UVB-induced lipid peroxidation and stress signaling (JNK and p38 activation) in human lens epithelial cells [86].

The antioxidant effect of AST also imparts as a neuroprotective effect against glutamate-induced RGC apoptosis [85]. In a previous study, AST protected the RGCs from apoptosis and damage via decreasing ROS production. The retinal oxidative DNA damage and lipid peroxidation damage were also mitigated [58]. Yamagishi et al. reported that AST reduced the ROS production. Moreover, the generation of the DNA damage marker, 8-OHdG, could inhibit apoptotic and RGC necrosis caused by glutamate, hypoxia, and oxidative stress [84].

Several studies have shown that AST prevents DES through antioxidative and anti-inflammatory effects [88]. Chronic inflammation and oxidative stress have been shown to play a role in DES [89, 90]. Free radicals attack the cellular plasma membrane and can cause corneal epithelial cell damage and death. They also damage the epithelial tissues of the conjunctiva, the lacrimal glands, and tear secreting tissues [91]. Antioxidants protect against free radicals and provide a stable tear film [92]. Furthermore, reports on AST treatment have shown that it prevents aging-related hyposalivation due to dysfunction of the submandibular glands

by decreasing inflammatory cells and increasing aquaporin-5 positive cells. Shimokawa et al. confirmed that upregulation of age-related markers, such as p53 and p21, increases intracellular ROS and oxidative stress, thereby leading to the development of DES. AST not only directly inhibited the generation of ROS in corneal epithelium cells in an in vitro model of dry eye syndrome, but also decreased the level of age-related markers, such as p53, p21, and p16, which were known to induce the generation of intracellular ROS and apoptosis of human corneal epithelial cells. Their results demonstrated that high affinity liposomal AST could be a potential candidate for the treatment of dry eyes [85].

4. Conclusion

AST, as a natural extract with strong antioxidative activity, can delay the progress of many diseases and protect multiple organs of the whole body. Toxicological analysis showed that the compound had good safety and bioavailability [93]. Although not officially approved by EFSA or FDA, AST has tremendous potential in the global health product market. AST is a promising ophthalmic drug. Most ophthalmic diseases, such as dry eye syndrome, keratitis, cataract, and age-related macular degeneration, are associated with oxidative stress and inflammation that lead to the production of reactive intermediates and cell apoptosis. In addition, ultraviolet radiation, chemotherapy, and other processes can induce retinal cell apoptosis. In this article, we reviewed the protective mechanism of AST in ophthalmic diseases (Figure 1). Further in-depth studies employing animal models or cell lines will be beneficial.

Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

YL Wang mainly contributed in study design and manuscript revision; M Yang mainly did the literature search and wrote the manuscript; both authors read and approved the final manuscript.

Acknowledgments

References

[1] H. Hashimoto, K. Arai, S. Hayashi, H. Okamoto, J. Takahashi, and M. Chikuda, "The effect of astaxanthin on vascular endothelial growth factor (VEGF) levels and peroxidation reactions in the aqueous humor," *Journal of Clinical Biochemistry & Nutrition*, vol. 59, no. 1, pp. 10–15, 2016.

[2] J. Hu, D. Nagarajan, Q. Zhang, J. S. Chang, and D. J. Lee, "Heterotrophic cultivation of microalgae for pigment production: A review," *Biotechnology Advances*, vol. 36, no. 1, pp. 54–67, 2018.

[3] Z. Yaqoob, M. S. Arshad, M. Imran et al., "Mechanistic role of astaxanthin derived from shrimp against certain metabolic disorders," *Food Sciences and Nutrition*, vol. 10, no. 1, pp. 12–20, 2021.

[4] J. S. Stewart, A. Lignell, A. Pettersson, E. Elfving, and M. Soni, "Safety assessment of astaxanthin-rich microalgae biomass: Acute and subchronic toxicity studies in rats," *Food and Chemical Toxicology*, vol. 46, no. 9, pp. 3030–3036, 2008.

[5] A. Imai, Y. Oda, N. Ito et al., "Effects of Dietary Supplementation of Astaxanthin and sesamin on daily fatigue: A Randomized, Double-blind, placebo-controlled, two-way crossover Study," *Nutrients*, vol. 10, no. 3, p. 281, 2018.

[6] T. Matsuno, "Cheminform abstract: xanthophylls as precursors of retinoids," *Cheminform*, vol. 22, no. 14, 2010.

[7] J. A. Edwards, P. Bellion, P. Beilstein, R. Rumbeli, and J. Schierle, "Review of genotoxicity and rat carcinogenicity investigations with astaxanthin," *Regulatory Toxicology and Pharmacology*, vol. 75, pp. 5–19, 2016.

[8] T. Nakano, M. Tosa, and M. Takeuchi, "Improvement of biochemical features in fish health by Red yeast and synthetic astaxanthin," *Journal of Agricultural and Food Chemistry*, vol. 43, no. 6, pp. 1570–1573, 1995.

[9] S. Fakhri, F. Abbaszadeh, L. Dargahi, and M. Jorjani, "Astaxanthin: A mechanistic review on its biological activities and health benefits," *Pharmacological Research*, vol. 136, pp. 1–20, 2018.

[10] S. Davinelli, L. Saso, F. D'Angeli, V. Calabrese, M. Intrieri, and G. Scapagnini, "Astaxanthin as a modulator of Nrf2, NF-κB, and their crosstalk: molecular mechanisms and possible clinical Applications," *Molecules*, vol. 27, no. 2, p. 502, 2022.

[11] R. Janani, R. E. Anitha, M. K. Perumal, P. Divya, and V. Baskaran, "Astaxanthin mediated regulation of VEGF through HIF1α and XBP1 signaling pathway: An insight from ARPE-19 cell and streptozotocin mediated diabetic rat model," *Experimental Eye Research*, vol. 206, Article ID 108555, 2021.

[12] A. Cort, N. Ozturk, D. Akpinar et al., "Suppressive effect of astaxanthin on retinal injury induced by elevated intraocular pressure," *Regulatory Toxicology and Pharmacology*, vol. 58, no. 1, pp. 121–130, 2010.

[13] F. Harada, T. Morikawa, A. Lennikov et al., "Protective effects of oral Astaxanthin nanopowder against ultraviolet-induced photokeratitis in mice," *Oxidative Medicine and Cellular Longevity*, vol. 2017, pp. 1–13, 2017.

[14] J. Y. Huang, P. T. Yeh, and Y. C. Hou, "A randomized, double-blind, placebo-controlled study of oral antioxidant supplement therapy in patients with dry eye syndrome," *Clinical Ophthalmology*, vol. 10, pp. 813–820, 2016.

[15] K. Izumi-Nagai, N. Nagai, K. Ohgami et al., "Inhibition of choroidal neovascularization with an anti-inflammatory carotenoid astaxanthin," *Investigative Ophthalmology & Visual Science*, vol. 49, no. 4, pp. 1679–1685, 2008.

[16] L. Y. Dong, J. Jin, G. Lu, and X. L. Kang, "Astaxanthin attenuates the apoptosis of retinal ganglion cells in db/db mice by inhibition of oxidative stress," *Marine Drugs*, vol. 11, no. 12, pp. 960–974, 2013.

[17] M. Yiğit, A. Güneş, C. Uğuz et al., "Effects of astaxanthin on antioxidant parameters in ARPE-19 cells on oxidative stress model," *International Journal of Ophthalmology*, vol. 12, no. 6, pp. 930–935, 2019.

[18] M. Valko, D. Leibfritz, J. Moncol, M. T. Cronin, M. Mazur, and J. Telser, "Free radicals and antioxidants in normal physiological functions and human disease," *The International Journal of Biochemistry & Cell Biology*, vol. 39, no. 1, pp. 44–84, 2007.

[19] H. Najafi, S. Changizi Ashtiyani, S. A. Sayedzadeh, Z. Mohamadi Yarijani, and S. Fakhri, "Therapeutic effects of curcumin on the functional disturbances and oxidative stress induced by renal ischemia/reperfusion in rats," *Avicenna J Phytomed*, vol. 5, no. 6, pp. 576–586, 2015.

[20] H. Wu, H. Niu, A. Shao et al., "Astaxanthin as a potential neuroprotective Agent for neurological Diseases," *Marine Drugs*, vol. 13, no. 9, pp. 5750–5766, 2015.

[21] C. Galasso, I. Orefice, P. Pellone et al., "On the neuroprotective Role of Astaxanthin: new perspectives?" *Marine Drugs*, vol. 16, no. 8, p. 247, 2018.

[22] Y. Feng, A. Chu, Q. Luo, M. Wu, X. Shi, and Y. Chen, "The protective effect of astaxanthin on cognitive function via inhibition of oxidative Stress and inflammation in the brains of chronic T2DM Rats," *Frontiers in Pharmacology*, vol. 9, p. 748, 2018.

[23] B. S. Kamath, B. M. Srikanta, S. M. Dharmesh, R. Sarada, and G. A. Ravishankar, "Ulcer preventive and antioxidative properties of astaxanthin from Haematococcus pluvialis," *European Journal of Pharmacology*, vol. 590, no. 1-3, pp. 387–395, 2008.

[24] L. Wu, W. Mo, J. Feng et al., "Astaxanthin attenuates hepatic damage and mitochondrial dysfunction in non-alcoholic fatty liver disease by up-regulating the FGF21/PGC-1α pathway," *British Journal of Pharmacology*, vol. 177, no. 16, pp. 3760–3777, 2020.

[25] N. P. Turrin and S. Rivest, "Molecular and cellular immune mediators of neuroprotection," *Molecular Neurobiology*, vol. 34, no. 3, pp. 221–242, 2006.

[26] G. C. Brown and J. J. Neher, "Inflammatory neurodegeneration and mechanisms of microglial killing of neurons," *Molecular Neurobiology*, vol. 41, no. 2-3, pp. 242–247, 2010.

[27] M. Balietti, S. R. Giannubilo, B. Giorgetti et al., "The effect of astaxanthin on the aging rat brain: gender-related differences in modulating inflammation," *Journal of the Science of Food and Agriculture*, vol. 96, no. 2, pp. 615–618, 2016.

[28] S. Kumar and S. V. Singh, "Inhibition of NF-κB signaling pathway by Astaxanthin supplementation for prevention of heat stress-induced inflammatory changes and apoptosis in Karan Fries heifers," *Tropical Animal Health and Production*, vol. 51, no. 5, pp. 1125–1134, 2019.

[29] M. Y. Li, L. Sun, X. T. Niu et al., "Astaxanthin protects lipopolysaccharide-induced inflammatory response in *Channa argus* through inhibiting NF-κB and MAPKs signaling pathways," *Fish & Shellfish Immunology*, vol. 86, pp. 280–286, 2019.

[30] X. Cai, Y. Chen, X. Xie, D. Yao, C. Ding, and M. Chen, "Astaxanthin prevents against lipopolysaccharide-induced acute lung injury and sepsis via inhibiting activation of MAPK/NF-κB," *American Journal of Translational Research*, vol. 11, no. 3, pp. 1884–1894, 2019.

[31] S. H. Kim, J. W. Lim, and H. Kim, "Astaxanthin inhibits mitochondrial Dysfunction and interleukin-8 expression in Helicobacter pylori-infected gastric epithelial cells," *Nutrients*, vol. 10, no. 9, p. 1320, 2018.

[32] J. H. Han, J. H. Ju, Y. S. Lee et al., "Astaxanthin alleviated ethanol-induced liver injury by inhibition of oxidative stress and inflammatory responses via blocking of STAT3 activity," *Scientific Reports*, vol. 8, no. 1, Article ID 14090, 2018.

[33] M. A. Grossman, C. Hofmann, H. L. Ng, and O. O. Yang, "Suboptimal stimulation by weak agonist epitope variants does not drive dysfunction of HIV-1-specific cytotoxic T lymphocyte clones," *AIDS*, vol. 33, no. 10, pp. 1565–1574, 2019.

[34] S. Katsiougiannis, R. Tenta, and F. N. Skopouli, "Autoimmune epithelitis (Sjögren's syndrome); the impact of metabolic status of glandular epithelial cells on auto-immunogenicity," *Journal of Autoimmunity*, vol. 104, Article ID 102335, 2019.

[35] H. An, N. G. Williams, and T. A. Shelkovnikova, "NEAT1 and paraspeckles in neurodegenerative diseases: A missing lnc found?" *Non-coding RNA Research*, vol. 3, no. 4, pp. 243–252, 2018.

[36] Y. Yang, W. Gao, S. Tao et al., "ER-mediated anti-tumor effects of shikonin on breast cancer," *European Journal of Pharmacology*, vol. 863, Article ID 172667, 2019.

[37] K. Kavitha, J. Kowshik, T. K. K. Kishore, A. B. Baba, and S. Nagini, "Astaxanthin inhibits NF-κB and Wnt/β-catenin signaling pathways via inactivation of Erk/MAPK and PI3K/Akt to induce intrinsic apoptosis in a hamster model of oral cancer," *Biochimica et Biophysica Acta (BBA) - General Subjects*, vol. 1830, no. 10, pp. 4433–4444, 2013.

[38] J. Kowshik, R. Nivetha, S. Ranjani et al., "Astaxanthin inhibits hallmarks of cancer by targeting the PI3K/NF-κB/STAT3 signalling axis in oral squamous cell carcinoma models," *IUBMB Life*, vol. 71, no. 10, pp. 1595–1610, 2019.

[39] Y. Xu, S. Yao, D. Gao, W. Li, D. Zheng, and Q. Zhang, "Effect of astaxanthin on apoptosis of rat renal tubular epithelial cells induced by iohexol," *American Journal of Translational Research*, vol. 11, no. 5, pp. 3039–3047, 2019.

[40] Y. M. A. Naguib, "Antioxidant activities of astaxanthin and related carotenoids," *Journal of Agricultural and Food Chemistry*, vol. 48, no. 4, pp. 1150–1154, 2000.

[41] K. H. Lin, K. C. Lin, W. J. Lu, P. A. Thomas, T. Jayakumar, and J. R. Sheu, "Astaxanthin, a carotenoid, stimulates immune Responses by enhancing IFN-γ and IL-2 Secretion in primary cultured lymphocytes in vitro and ex vivo," *International Journal of Molecular Sciences*, vol. 17, no. 1, p. 44, 2015.

[42] L. Tian, Y. Wen, S. Li et al., "Benefits and Safety of Astaxanthin in the treatment of mild-to-moderate Dry eye Disease," *Frontiers in Nutrition*, vol. 8, Article ID 796951, 2021.

[43] V. Parisi, M. Tedeschi, G. Gallinaro, M. Varano, S. Saviano, and S. Piermarocchi, "Carotenoids and Antioxidants in Age-Related maculopathy Italian Study," *Ophthalmology*, vol. 115, no. 2, pp. 324–333, 2008.

[44] A. Lennikov, N. Kitaichi, R. Fukase et al., "Amelioration of ultraviolet-induced photokeratitis in mice treated with astaxanthin eye drops," *Molecular Vision*, vol. 18, pp. 455–464, 2012.

[45] S. Piermarocchi, S. Saviano, V. Parisi et al., "Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study," *European Journal of Ophthalmology*, vol. 22, no. 2, pp. 216–225, 2012.

[46] D. A. Schaumberg, D. A. Sullivan, J. E. Buring, and M. Dana, "Prevalence of dry eye syndrome among US women," *American Journal of Ophthalmology*, vol. 136, no. 2, pp. 318–326, 2003.

[47] M. Votruba and Z. Gregor, "Neovascular age-related macular degeneration: present and future treatment options," *Eye*, vol. 15, no. 3, pp. 424–429, 2001.

[48] T. Otsuka, M. Shimazawa, T. Nakanishi et al., "The protective effects of a Dietary carotenoid, Astaxanthin, Against light-induced Retinal Damage," *Journal of Pharmacological Sciences*, vol. 123, no. 3, pp. 209–218, 2013.

[49] H. Hashimoto, K. Arai, J. Takahashi, and M. Chikuda, "Effects of astaxanthin on VEGF level and antioxidation in human aqueous humor: difference by sex," *Journal of Clinical Biochemistry & Nutrition*, vol. 65, no. 1, pp. 47–51, 2019.

[50] M. Saito, K. Yoshida, W. Saito et al., "Astaxanthin increases choroidal blood flow velocity," *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 250, no. 2, pp. 239–245, 2012.

[51] M. Yang, Y. Chen, T. Zhao, and Z. Wang, "Effect of astaxanthin on metabolic cataract in rats with type 1 diabetes mellitus," *Experimental and Molecular Pathology*, vol. 113, Article ID 104372, 2020.

[52] Y. Inoue, M. Shimazawa, R. Nagano et al., "Astaxanthin analogs, adonixanthin and lycopene, activate Nrf2 to prevent light-induced photoreceptor degeneration," *Journal of Pharmacological Sciences*, vol. 134, no. 3, pp. 147–157, 2017.

[53] T. Otsuka, M. Shimazawa, Y. Inoue et al., "Astaxanthin protects Against Retinal Damage: evidence from in vivo and in vitro Retinal ischemia and Reperfusion models," *Current Eye Research*, vol. 41, no. 11, pp. 1465–1472, 2016.

[54] S. Ishikawa, K. Hashizume, H. Nishigori, Y. Tezuka, A. Sanbe, and D. Kurosaka, "Effect of astaxanthin on cataract formation induced by glucocorticoids in the chick embryo," *Current Eye Research*, vol. 40, no. 5, pp. 535–540, 2015.

[55] B. Baccouche, M. Benlarbi, A. J. Barber, and R. Ben Chaouacha-Chekir, "Short-term Administration of Astaxanthin Attenuates Retinal changes in diet-induced Diabetic psammomys obesus," *Current Eye Research*, vol. 43, no. 9, pp. 1177–1189, 2018.

[56] P. T. Yeh, H. W. Huang, C. M. Yang, and C. H. Yang, "Astaxanthin inhibits expression of Retinal oxidative Stress and inflammatory mediators in Streptozotocin-induced Diabetic Rats," *PLoS One*, vol. 11, no. 1, Article ID e0146438, 2016.

[57] A. Küçüködük, F. Helvacioglu, N. Haberal et al., "Anti-proliferative and anti-apoptotic effect of astaxanthin in an oxygen-induced retinopathy mouse model," *Canadian Journal of Ophthalmology*, vol. 54, no. 1, pp. 65–74, 2019.

[58] M. Kuraji, T. Matsuno, and T. Satoh, "Astaxanthin affects oxidative stress and hyposalivation in aging mice," *Journal of Clinical Biochemistry & Nutrition*, vol. 59, no. 2, pp. 79–85, 2016.

[59] K. Kikuchi, Z. Dong, Y. Shinmei et al., "Cytoprotective effect of astaxanthin in a model of normal intraocular pressure glaucoma," *Journal of Ophthalmology*, vol. 2020, Article ID 9539681, 6 pages, 2020.

[60] F. Hüseyin, T. Levent, A. Yılmaz et al., "The protective effects of AST against cisplatin-induced retinal toxicity," *Cutaneous and Ocular Toxicology*, vol. 38, pp. 59–65, 2019.

[61] T. Pauloin, M. Dutot, F. Joly, J. M. Warnet, and P. Rat, "High molecular weight hyaluronan decreases UVB-induced apoptosis and inflammation in human epithelial corneal cells," *Molecular Vision*, vol. 15, pp. 577–583, 2009.

[62] M. Norval, "The mechanisms and consequences of ultraviolet-induced immunosuppression in the skin and eye," *Eye and Contact Lens: Science and Clinical Practice*, vol. 37, no. 4, pp. 176–184, 2011.

[63] T. Tenkate, B. Adam, R. H. Al-Rifai et al., "WHO/ILO work-related burden of disease and injury: protocol for systematic reviews of occupational exposure to solar ultraviolet radiation and of the effect of occupational exposure to solar ultraviolet radiation on cataract," *Environment International*, vol. 125, pp. 542–553, 2019.

[64] J. Y. Hu, L. Yan, Y. D. Chen et al., "Population-based survey of prevalence, causes, and risk factors for blindness and visual impairment in an aging Chinese metropolitan population," *International Journal of Ophthalmology*, vol. 10, no. 1, pp. 140–147, 2017.

[65] A. Vurmaz, R. Duman, M. C. Sabaner, T. Ertekin, and A. Bilir, "Antioxidant effects of piperine in in-vivo chick embryo cataract model induced by steroids," *Cutaneous and Ocular Toxicology*, vol. 38, no. 2, pp. 182–189, 2019.

[66] M. Mrowicka, J. Mrowicki, J. P. Szaflik, M. Szaflik, M. Ulinska, and I. Majsterek, "Analysis of antioxidative factors related to AMD risk development in the polish patients," *Acta Ophthalmologica*, vol. 95, no. 5, pp. 530–536, 2017.

[67] I. Ahiskali, C. L. Pinar, M. Kiki et al., "Effect of taxifolin on development of retinopathy in alloxan-induced diabetic rats," *Cutaneous and Ocular Toxicology*, vol. 38, no. 3, pp. 227–232, 2019.

[68] F. Guo, T. Zhou, J. Tang, M. Dong, and Q. Wei, "Related Risk factors between subclinical carotid atherosclerosis and Diabetic Retinopathy in newly diagnosed type 2 Diabetes mellitus in China," *Experimental and Clinical Endocrinology & Diabetes*, vol. 129, no. 04, pp. 283–288, 2021.

[69] M. S. Ola, A. S. Alhomida, and K. F. LaNoue, "Gabapentin Attenuates oxidative Stress and Apoptosis in the Diabetic Rat Retina," *Neurotoxicity Research*, vol. 36, no. 1, pp. 81–90, 2019.

[70] N. S. Sahajpal, R. K. Goel, A. Chaubey, R. Aurora, and S. K. Jain, "Pathological perturbations in Diabetic Retinopathy: hyperglycemia, AGEs, oxidative Stress and inflammatory pathways," *Current Protein & Peptide Science*, vol. 20, no. 1, pp. 92–110, 2018.

[71] A. Roohbakhsh, G. Karimi, and M. Iranshahi, "Carotenoids in the treatment of diabetes mellitus and its complications: A mechanistic review," *Biomedicine & Pharmacotherapy*, vol. 91, pp. 31–42, 2017.

[72] X. Zhang, R. Zhang, and J. Wu, "Inhibition of the NR2B-PSD95 interaction exerts neuroprotective effects on Retinal ischemia-Reperfusion injury," *Neuroscience*, vol. 490, pp. 89–99, 2022.

[73] M. Renner, G. Stute, M. Alzureiqi et al., "Optic nerve Degeneration after Retinal ischemia/Reperfusion in a rodent model," *Frontiers in Cellular Neuroscience*, vol. 11, p. 254, 2017.

[74] H. Seong, J. Ryu, W. S. Yoo et al., "Resveratrol ameliorates Retinal ischemia/Reperfusion injury in C57BL/6J mice via Downregulation of caspase-3," *Current Eye Research*, vol. 42, no. 12, pp. 1650–1658, 2017.

[75] E. Matthé, P. Eulitz, and O. Furashova, "Acute retinal ischemia IN central versus branch retinal artery occlusion: changes in Retinal layers' thickness on spectral-domain optical coherence tomography in Different grades of Retinal ischemia," *Retina*, vol. 40, no. 6, pp. 1118–1123, 2020.

[76] J. Mercke Odeberg, A. Lignell, A. Pettersson, and P. Hoglund, "Oral bioavailability of the antioxidant astaxanthin in humans is enhanced by incorporation of lipid based formulations,"

European Journal of Pharmaceutical Sciences, vol. 19, no. 4, pp. 299–304, 2003.

[77] S. E. Moroi, D. M. Reed, D. S. Sanders et al., "Precision medicine to prevent glaucoma-related blindness," *Current Opinion in Ophthalmology*, vol. 30, no. 3, pp. 187–198, 2019.

[78] J. P. Renard, J. R. Fénolland, and J. M. Giraud, "Glaucoma progression analysis by spectral-domain optical coherence tomography (SD-OCT)," *Journal Français d'Ophtalmologie*, vol. 42, no. 5, pp. 499–516, 2019.

[79] Y. Li, Q. Wang, C. Chu, and S. Liu, "Astaxanthin protects retinal ganglion cells from acute glaucoma via the Nrf2/HO-1 pathway," *Journal of Chemical Neuroanatomy*, vol. 110, Article ID 101876, 2020.

[80] L. Zhang, K. Ohgami, Y. Cheng et al., "Docetaxel maintenance therapy versus best supportive care after first-line chemotherapy with different dose docetaxel plus cisplatin for advanced non-small cell lung cancer (TFINE study, CTONG-0904): an open-label, randomized, phase III trial," *Annals of Translational Medicine*, vol. 9, no. 4, p. 338, 2021.

[81] A. E. Ibrahim, M. W. Shafaa, M. H. Khedr, and R. F. Rashed, "Comparative study between lutein and its liposomal form on cisplatin-induced retinal injury in rabbits," *Cutaneous and Ocular Toxicology*, vol. 38, no. 3, pp. 279–285, 2019.

[82] M. Khedr, N. Barakat, I. Mohey El-Deen, and F. Zahran, "Impact of preconditioning stem cells with all-trans retinoic acid signaling pathway on cisplatin-induced nephrotoxicity by down-regulation of TGFβ1, IL-6, and caspase-3 and up-regulation of HIF1α and VEGF," *Saudi Journal of Biological Sciences*, vol. 29, no. 2, pp. 831–839, 2022.

[83] C. W. Lin, C. M. Yang, and C. H. Yang, "Protective effect of Astaxanthin on blue light light-emitting Diode-induced Retinal cell Damage via free Radical Scavenging and Activation of PI3K/Akt/Nrf2 pathway in 661W cell model," *Marine Drugs*, vol. 18, no. 8, p. 387, 2020.

[84] R. Yamagishi and M. Aihara, "Neuroprotective effect of astaxanthin against rat retinal ganglion cell death under various stresses that induce apoptosis and necrosis," *Molecular Vision*, vol. 20, pp. 1796–1805, 2014.

[85] T. Shimokawa, M. Yoshida, T. Fukuta, T. Tanaka, T. Inagi, and K. Kogure, "Efficacy of high-affinity liposomal astaxanthin on up-regulation of age-related markers induced by oxidative stress in human corneal epithelial cells," *Journal of Clinical Biochemistry & Nutrition*, vol. 64, no. 1, pp. 27–35, 2019.

[86] C. Chitchumroonchokchai, J. A. Bomser, J. E. Glamm, and M. L. Failla, "Xanthophylls and alpha-tocopherol decrease UVB-induced lipid peroxidation and stress signaling in human lens epithelial cells," *Journal of Nutrition*, vol. 134, no. 12, pp. 3225–3232, 2004.

[87] Z. Li, X. Dong, H. Liu et al., "Astaxanthin protects ARPE-19 cells from oxidative stress via upregulation of Nrf2-regulated phase II enzymes through activation of PI3K/Akt," *Molecular Vision*, vol. 19, pp. 1656–1666, 2013.

[88] Y. Nakajima, Y. Inokuchi, M. Shimazawa, K. Otsubo, T. Ishibashi, and H. Hara, "Astaxanthin, a dietary carotenoid, protects retinal cells against oxidative stress in-vitro and in mice in-vivo," *Journal of Pharmacy and Pharmacology*, vol. 60, no. 10, pp. 1365–1374, 2010.

[89] A. J. Augustin, M. Spitznas, N. Kaviani et al., "Oxidative reactions in the tear fluid of patients suffering from dry eyes," *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 233, no. 11, pp. 694–698, 1995.

[90] J. Ling, B. C. L. Chan, M. S. M. Tsang et al., "Current Advances in mechanisms and treatment of Dry eye Disease: toward Anti-inflammatory and immunomodulatory therapy and traditional Chinese medicine," *Frontiers of Medicine*, vol. 8, Article ID 815075, 2022.

[91] Y. J. Li, L. J. Luo, S. G. Harroun et al., "Synergistically dual-functional nano eye-drops for simultaneous anti-inflammatory and anti-oxidative treatment of dry eye disease," *Nanoscale*, vol. 11, no. 12, pp. 5580–5594, 2019.

[92] E. I. Postorino, P. Aragona, L. Rania et al., "Changes in conjunctival epithelial cells after treatment with 0.2% xanthan gum eye drops in mild-moderate dry eye," *European Journal of Ophthalmology*, vol. 30, no. 3, pp. 439–445, 2020.

[93] EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), V. Bampidis, G. Azimonti et al., "Safety and efficacy of astaxanthin-dimethyldisuccinate (Carophyll® Stay-Pink 10%-CWS) for salmonids, crustaceans and other fish," *EFSA Journal*, vol. 17, no. 12, Article ID e05920, 2019.