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Review Article

Herb-derived Compounds and Other Potential Molecules for Non-exudative Age-related Macular Degeneration (AMD): A Systematic Review

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ABSTRACT

This article aims to systematically review published research articles on investigating and developing herbs, herb-derived compounds, and other molecules for treating age-related macular degeneration (AMD), a neurodegenerative disorder. Systematic literature searches were conducted in three electronic databases: PubMed, ScienceDirect, and Google Scholar. A total of 84 research articles that met the eligibility criteria were included in the analysis. Fifty-two and thirty articles are related to herbs/herb-derived compounds and non-herbal molecules. Two articles are related to both categories. Most compounds, except emixustat, demonstrated protective activities against retinal cell damage. These protective effects primarily stem from their antioxidant, anti-inflammatory, and anti-apoptotic properties, involving various molecular targets and signaling pathways. Dietary carotenoids, polyphenols and diarylheptanoids, particularly those containing saffron, curcumin, lutein, zeaxanthin, quercetin, and resveratrol, hold promise as herb-derived compounds to prevent and delay the onset of AMD development. Additionally, novel strategies include compounds that inhibit RPE65, a key enzyme in the visual cycle, those targeting pyroptosis-mediated inflammation and cell death, and those addressing angiogenesis processes in the retina. These research avenues offer hope for the development of effective treatments for AMD.

Keywords:
Age-related macular degeneration (AMD), Biomolecules, Herbs, Herb-derived compounds, Non-herbal molecules

1. INTRODUCTION

Age-related macular degeneration (AMD) is a multifactorial neurodegenerative disorder that damages the macular, the central and most vital area of the retina, leading to the loss of central vision by modulating different physiological pathways. It is one of the leading causes of permanent visual damage and blindness in the elderly[1]. Early-stage AMD is characterized by lipofuscin accumulation in the retinal pigment epithelium (RPE) and drusen (yellowish-white deposits) deposition in the Bruch's membrane (**Figure 1**). Late-stage AMD comprises two distinct types: wet AMD (neovascular or exudative) and dry AMD (non-neovascular or non-exudative).). Exudative AMD is characterized by choroidal neovascularization in the retina, resulting in rapid vision loss[2].

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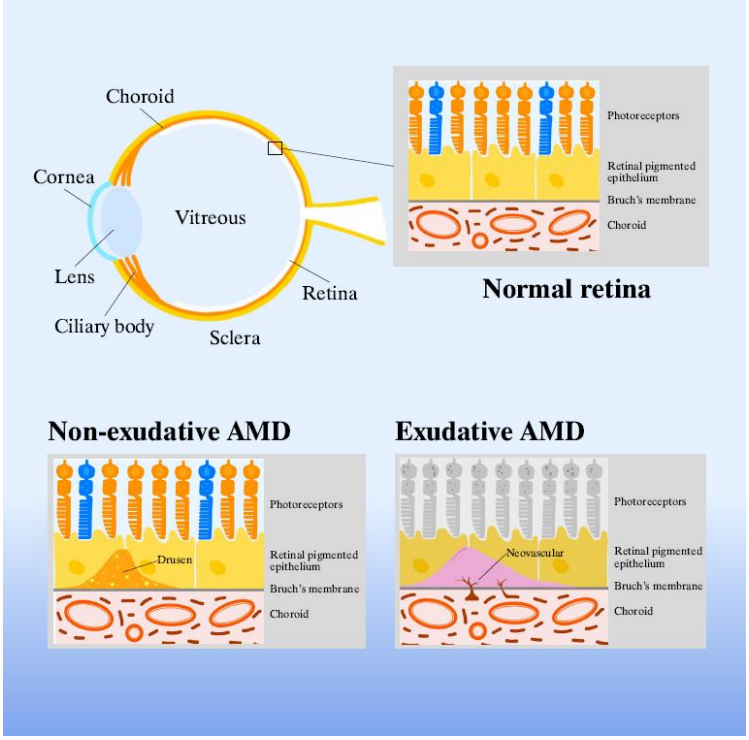

Figure 1. A cross-sectional diagram of the retina, including the layers and the changes related to age-related macular degeneration (AMD). It highlights the photoreceptor layer, retinal pigment epithelium (RPE), Bruch's membrane, and choroid, with key features of AMD like drusen deposits and abnormal blood vessel growth.

Non-exudative AMD is a slow-progressing disease characterized by subretinal pigment epithelium drusen deposits and the geographic atrophy of the RPE. Although RPE pathology is considered the primary lesion in AMD [3], dysfunction and photoreceptor death account for vision loss. Various conditions, including genetic predisposition, smoking, exposure to sunlight, and ageing, may contribute to a functional decline of the all-*trans*-retinal clearance and macular degeneration[4]. Several epidemiologic studies suggest that long-term exposure to light (blue and white light) may impact the incidence of AMD[5]. With the popularization of human electronic products, the risk of blue light (BL) is increasing. Care for earlier-stage AMD and dry AMD is limited to risk factor management. Smoking cessation, weight reduction, and specific vitamins and nutrient supplements may help to slow disease progression[6]. Antivascular endothelial growth factor (VEGF) agents are the primary treatment for suppressing choroidal neovascularization in exudative AMD, which has shown significant improvement in central vision loss[7-9]. Nevertheless, current therapies to restore lost vision in eyes with advanced non-exudative AMD are lacking, and effective therapeutic options are urgently needed.

The retinoid visual cycle is a series of biochemical reactions of retinoids in ocular tissues that begin when a photon of light interacts with the visual pigment protein rhodopsin, resulting in an electrophysiological signal and visual perception. The process proceeds with several reactions that lead to the generation of rhodopsin molecules. The light-sensitive visual chromophore, 11-*cis*-retinal, is initially synthesized, and several retinoid metabolizing enzymes and retinoid-binding proteins are involved in the regeneration of the rhodopsin. The cycle regenerates 11-*cis*-retinal and eliminates its toxic byproducts from the retina, supporting visual function and retinal neuron survival. In non-exudative AMD, drusen, a pathological feature of dry AMD, contains lipofuscin and its component, a fluorescent substance called bis-retinoid *N*-retinyl-*N*-retinylidene ethanolamine (A2E), which are toxic lipid byproducts of 11-*cis*-retinal that damage RPE cells[10-16]. A2E consists of all-*trans*-retinal and ethanolamine in a 2:1 ratio. With ageing, photoactive A2E accumulates between the RPE cell layer and Bruch's membrane in the lysosomes around the nucleus of RPE cells, inducing inflammation, apoptosis and angiogenesis of the cells[17]. Once exposed to BL, a component of natural light, A2E acts as a photosensitizer that induces the production of reactive oxygen species (ROS) and other toxic products, triggering RPE cell damage[17]. ROS further attack A2E to induce photooxidation and photodegradation, which provoke the formation of advanced glycation end products (AGEs) that cause RPE cell dysfunction, inflammation, and apoptosis[18-19]. Therefore, A2E accumulation in the retina is a prominent marker, and BL-induced photo-oxidative damage of A2E is a significant risk factor in non-exudative AMD. Besides natural light, BL exposure is an essential factor contributing to AMD. Due to its short wavelength (400-450 nm) absorbance, BL can directly penetrate the lens and reach the retina, causing retinal damage. Thus, finding compounds that can protect

against light and A2E stresses in the retina could provide potential therapies for AMD. This article systematically reviews published articles on research and development of herbal products and synthetic molecules for AMD therapy.

2. MATERIALS AND METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20].

2.1. Database and search strategy

The literature search was conducted from three databases, i.e., PubMed, ScienceDirect, and Scopus, from May 1 to December 31, 2023. The search terms applied were "AMD" AND "Herbs" AND/OR "compounds" AND/OR "Biologics" AND/OR "acute macular degeneration" AND/OR "AMD". All articles were retrieved and downloaded to the EndNote X9 database (Thomson Reuters Company, Canada) for further analysis.

2.2. Study selection

Study selection was performed independently by two reviewers. Identified articles were initially screened by titles and abstracts to exclude irrelevant articles and duplication. Full-text articles included after the screening were further evaluated by applying the predefined eligibility criteria. Studies were eligible if they met the following criteria: (i) They were published up to December 2023, (ii) They were available as full-texts in English, and (iii) They involved *in vitro, in vivo,* or clinical studies related to the investigation of potential herbal and non-herbal products for prevention of AMD. Articles were excluded if they met the following criteria: (i) They had unclear methodology or insufficient information, or (ii) They were review articles, letters to the editor, editorials, systematic analyses, or meta-analyses.

2.3. Data extraction

Two reviewers extracted data independently and resolved the disparity by discussion and suggestions from the third reviewer. The following information was extracted: first author's name and year of publication, name of herbs/herbal extract or isolated/synthetic analog(s)/derivatives/chemical compounds/biologics, type of study (*in vitro/in vivo*/clinical), study's objective(s), key findings, and conclusions.

3. RESULTS

A total of 544 articles from PubMed (n=86), ScienceDirect (n=449), and Google (n=9) were downloaded to the EndNote database. Among them, 21 articles were identified as duplicate records and were removed before screening. During the screening, 439 articles were excluded (244 review articles, 188 unrelated articles, 2 short communication articles, 3 articles published in non-English language, and 1 article with insufficient information). Finally, 84 articles were included in the analysis. The flow diagram of the study inclusion and exclusion is presented in **Figure 2.** The included articles are classified as i) herbs/herb-derived compounds (n=52: **Table 1**), ii) non-herbal molecules (n=30; **Table 2**), and iii) a mixture of i and ii (n=2: **Table 3**). The studies involving herbs/herb-derived compounds are classified according to chemical composition as Carotenoids (12 articles), flavonoids (10 articles), polyphenols (7 articles), diarylheptanoids (6 articles), anthocyanins (3 articles), stilbenoids (3 articles), terpenoids (3 articles), saponins (2 articles), iridoid glycosides (1 article), phenolic acid (1 article), protein (1 article), and mixed (3 articles). The studies involving non-herbal molecules are classified as chemical compounds (17 articles), biological compounds (4 articles), growth factors (3 articles), essential elements (2 articles), recombinant proteins (2 articles), stem cells (1 article), and intraocular lens (1 article).

Study models: The ARPE-19 cell line was commonly used in the *in vitro* model to investigate the molecular targets involved in the pathogenesis of AMD and identify new compounds to protect RPE cells against A2E oxidation[21-23]. Other *in vitro* models included microsomal bovine RPE[24], 661W murine photoreceptor cells[25], the retinal section from bovine eyes[26], RPE cells from pig eyes[27], microsomal bovine RPE65[28-29], human bone osteosarcoma epithelial (U2OS) cell[30], human primary RPE cells[30], and primary human HRPEpiC[31].

Most of the *in vivo* models used BALB/c mice. Other animal models were BALB/cJ albino mice[29,32], albino ddY mice[33], C57BL/6J mice[34], *cc/2/Cx3cr1-DKO rd8* knockout mice[30,35-40], 129/SvlmJ mice[41], *Abca4-/- Rdh8-/-* mice[30,42], albino Sprague Dawley rats[43], pigmented B6129SF2/J strain mice [44], pigmented rabbits[45], and ICR mice[46].

BL and A2E-induced retinal damage is the main approach used in the *in vitro* and *in vivo* models[17,22-44,46]. The white and bright light was also used[17,28,29,44]. The damage model of RPE cells induced by A2E and BL mimics the AMD pathogenesis in humans, thus accurately reflecting the physiological condition and the pathogenesis of retinal photooxidation. Apart from

A2E, chemical inducers used to induce retinal damage include H_2O_2 [35,52,67,68,73,93], paraquat[31], amyloid beta[85,88], lipopolysaccharide (LPS)[50,88], N-methyl-N-nitrosourea (NMU)[24], $NaIO_3$ [34,69], homocysteine[78], cobalt chloride[51], AtRA[30], and TNF-α[73].

Clinical studies involved healthy Caucasians aged more than 50 yr[87], middle-aged Taiwanese subjects[75], and patients with early and moderate AMD[80].

Fundamental laboratory techniques applied to assess the preventive effects of herbal products and other molecules included cell viability assay (MTT, CCK8, WST-1, LDH, and Hoechst 33342), ROS level (DCFDA, CM-H2DC-FDA, and ROS assay kit), antioxidant activity (DPPH and ABTS radical scavenging assays, FRAP assay, GSH & MDA levels, and GPx activity), gene expression (qRT-PCR), protein expression (Western blot), apoptosis (flow cytometry, caspase-3 and caspase-9 activity assays, and TUNEL assay), cell cycle analysis (flow cytometry and Tali-based cytometer), and cytokine levels were (ELISA). Protein localization/specific protein (immunohistochemistry, immunofluorescence), A2E level (HPLC, LC/MS/MS), A2E accumulation/degradation (HPLC, A2E-BDP fluorescence), histopathology (H&E); retinal morphology & lesion (fundoscopy, TEM, optical microscope, ophthalmological examination), retinal function (electroretinogram: ERG).

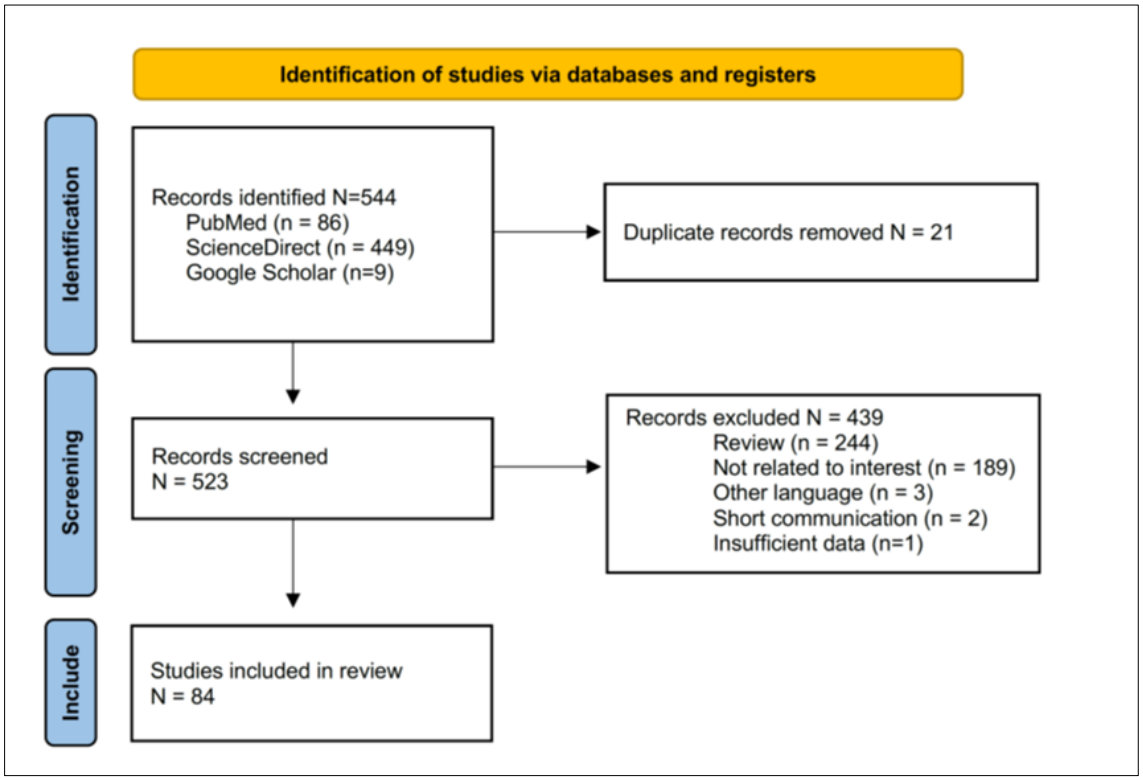

Figure 2. Flow diagram for identification and screening of eligible research articles relevant to research and development of potential candidates for AMD.

Table 1 Herbs and active constituents which have been investigated for their potential protective activities against AMD.

Ref	Compound/Extract	Objectives	Study models & Methodology	Main findings	Conclusions
Anthocyanin					
[25]	*Aristolelia chilensis* (Maqui berry extract: MBE) & its constituents [Delphinidin 3,5-O-diglucoside (D3G5G) & Delphinidin 3-O-sambubioside-5-O-glucoside (D3S5G)]	To examine the protective effects of MBE and its constituents (D3G5G & D3S5G) against light-induced murine photoreceptor cells.	***In vitro:*** Anthocyanins (HPLC); white fluorescence light-induced cell death in murine photoreceptor cells (661W); cell viability (WST-8, Hoechst 33342 & PI); ROS (DCFDA); protein expression (Western blot).	Eight anthocyanin components of MBE (higher contents with D3G5G & D3S5G). MBE, D3G5G, or D3S5G alone: no cytotoxic effects; significant inhibition of cell death, number of apoptotic cells & radical activity. MBE: significant inhibition of phosphorylation of p38 & cell death. Delphinidin (a main anthocyanidin in MBE): significant inhibition of cell death (stronger than malvidin & peonidin).	MBE & its anthocyanidins: suppression of the light-induced photoreceptor cell death by inhibiting ROS production, possibly through inhibition of phosphorylated-p38.
[76]	Cyanidin-3-glucoside	To investigate the effects of cyanidin-3-glucoside on BL & A2E-containing RPE cells. To explore the involvement of endoplasmic reticulum (ER) stress & downstream nuclear factor (erythroid-derived 2)-like 2 (Nrf2) in the mechanisms of action.	***In vitro:*** A2E/BL-induced epithelial degeneration in ARPE-19 cells: cell viability (WST-8); apoptosis (flow cytometry & TUNEL); paracellular permeability (TEER); gene expression (qRT-PCR); protein expression (Western blot, immunofluorescence); cell morphology (TEM).	Cyanidin-3-glucoside: increase of cell viability & inhibition of cell apoptosis; enhancement of the barrier function of RPE cells & upregulation of the expression of tight junction protein ZO-1; significant suppression of PERK/eIF2α/ATF4/CHOP pathway & maintenance of normal ER morphology; activation of Nrf2 pathway to promote RPE survival.	Cyanidin-3-glucoside: promotion of the barrier function of RPE cells by regulating ER stress-induced apoptosis, a new approach to preventing retinal diseases.
[73]	Delphinidin [2-(3,4,5-trihydroxyphenyl) chromenylium-3,5,7-triol] (from berry, red wine)	To evaluate the protective effects & underlying molecular mechanisms of action of delphinidin against H_2O_2-induced toxicity in human ARPE-19 cells.	***In vitro:*** H_2O_2-induced oxidative stress in ARPE-19 cells - cell viability (MTT); apoptosis (flow cytometry); ROS (DCFDA); oxidative & lipid oxidation biomarkers (SOD, CAT, GSH-PX & MDA; enzyme assay); protein expression (Western blot).	Delphinidin: no cytotoxicity; significant increase of cell viability; significant reduction of H_2O_2-induced cell apoptosis; decrease in the expression of Bax, cytochrome c & caspase-3; increase in Bcl-2 expression; attenuation of the expression of Nox1 protein (dose-dependent); no effect on MDA level & activities of SOD, CAT & GSH-PX; increase of MDA & decrease of activities of SOD, CAT & GSH-PX (concentration-dependent); increase of Nrf2 protein expression (concentration-dependent).	Delphinidin: effective protection of human ARPE-19 cells from H_2O_2-induced oxidative damage *via* anti-apoptotic & antioxidant effects.
Carotenoids					
[33]	Astaxanthin	To investigate the protective effects of astaxanthin against light-induced retinal damage *in vitro & in vivo.*	***In vivo:*** White light-induced retinal damage in albino ddY mice; ERG; histopathology (H&E); ONL thickness (light microscope); apoptosis (TUNEL); DNA oxidative damage (immunohistochemistry); gene expression (qRT-PCR).	Astaxanthin: inhibition of the reduction of a- & b-wave amplitudes; prevention of the reduction of ONL thickness; significant reduction of apoptosis; significant decrease of the number of DNA oxidative damage; no effect on the endogenous antioxidant genes Sod1, MT-II & MT-III.	Astaxanthin: protective effects against light-induced retinal damage, through suppressing ROS-induced cell apoptosis.

			In vitro: White light-induced retinal damage in mouse retinal cone-cell line 661W; cell viability (Hoechst 33342, PI); ROS (DCFDA).	Astaxanthin: protection against cell death (concentration-dependent); significant reduction of ROS production.	
[185]	*Crocus sativus* L. (Saffron)	To evaluate the functional effect of short-term supplementation of saffron in early AMD.	***Clinical:*** Cross-over, randomized trial in 25 patients with early AMD. Saffron oral supplement (20 mg/d) *vs.* Placebo over 3 months, then Placebo or Saffron for 3 months. Clinical exam; focal electroetinogram (fERG)-derived macular flicker sensitivity estinate.	fERG amplitude: significant increase by 0.25 log mV. fERG thresholds: significant decrease by -0.26 log unit.	Short-term Saffron supplementation: improvement of retinal flicker sensitivity in early AMD.
[186]	*Crocus sativus* L. (Saffron)	To evaluate the effect of saffron in extending functional benefits in early AMD.	***Clinical:*** Longitudinal, open-label study in 29 patients with early AMD, with baseline visual acuity > 0.3. Sffron oral supplement (20 mg/d) over 14 (+) 2 months. Clinical exam; focal electroetinogram (fERG)-derived macular flicker sensitivity estinate.	fERG sensitivity: significant improvement by 0.3 log units after 3 months, stable during follow-up. Visual acuity: significant improvement by 2 Snellen lines after 3 months, stable during follow-up.	Saffron oral supplement: improvement of macular function with extension over long-term follow-up.
[187]	*Crocus sativus* L. (Saffron)	To investigate the influence of genetic polymorphisms of complement factor on the neuroprotective effect of saffron supplements in early AMD.	***Clinical:*** 33 AMD patients screened for complement factor H (CFH) (rs1061170) & age-related maculopathy (ARMS2) (rs10490924) polymorphisms, receiving saffron oral supplementation (20 mg/d) for an average of 11 months (6-12). Clinical exam; focal electroetinogram (fERG)-derived macular flicker sensitivity estinate.	fERG amplitude & sensitivity: significant improvement after 3 months, stable during follow-up. No significant association between clinical & fERG improvements and FCH & ARMS2 genotypes.	No relationship between functional effect of saffron supplementation and CFH & ARMS2 genotypes.
[188]	*Crocus sativus* L. (Saffron)	To evaluate efficacy and safety of saffron in patients with wet or dry AMD.	***Clinical:*** Duble-Blind, placebo-controlled, randomized trial in 60 patients with wet or dry AMD. Oral saffron 30 mg/d or Placebo supplementation for 6 months. Optical coherence tomography (OCT); electroretinography (ERG); fluorescein angiography; visual acuity test.	Dry AMD: No significant decrease in OCT, but significant increase in ERG at 3 months; significant difference in OCT with wet AMD at follow-up. Wet AMD: significant decrease in OCT at follow-up compared with dry AMD; significant increase in ERG at 3 months compared with dry AMD.	Daily supplements with 30 mg of saffron for 6 months: a mid-term, significant improvement in retinal function in AMD.

[189]	*Crocus sativus* L. (Saffron)	To evaluate efiicacy & safety of oral saffron in mild/moderate AMD.	***Clinical:*** Randomized, double-blinded, placebo-controlled cross-over trial in 100 adults *aged > 50 yr) with mild/moderate AMD and vision > 20/70 Snellen equivalent in > 1 eye. Oral supplement: 20 mg/day for 3 months vs. Placebo for 3 months, followed by crossover for 3 months with/without Age-Related Eye Disease Study (AREDS) supplements. Changes in multifocal electroretinogram (mfERG) response density & latency; changes in best-corrected visual acuity (BCVA); safety outcomes; changes in mfERG & BCVA among participants on AREDS supplements and changes in microperimetry.	Saffron: improvement of BCVA by 0.69 letters; decrease in mfERG latency by 0.17 ms. Saffron + AREDS supplements: improvement of BCVA by 0.73 letters; decrease in mfERG density by 2.8%. No difference in incidence of adverse events.	Saffron supplements: modest improvement of visual function in AMD, including rhose using AREDS supplements.
[190]	*Crocus sativus* L. (Saffron)	To assess effects on saffron in AMD.	***In vivo:*** SD adult rats (light damaged), raised at 5 lux: Saffron; SDS-OAGE, western blotting, enzyme activity assay, immunolabelling. Clinical: AMD patients: Sffron (n=23(vs. Lutein/Zeaxanthin (n=19); ERG recording & clinical examination.	Saffron: stable visual function, while deterioration is present in Lutein/Zeaxanthin. MMP-3: decrease in LD saffron-treated retinas.	Sffron: neuroprotective activity.
[191]	*Crocus sativus* L. (Saffron)	To assess long-term efficacy & safety in mild/moderate AMD.	***Clinical:*** Open-label extension tria of 93 adults (aged > 50 yr) with mild/moderate AMD and vision >20/70 Snellen equivalent in > 1 eyes. Oral supplement: 20 mg/day for 12 months, with or without Age-Related Eye Diseases Study (AREDS) supplements. Changes in multifocal electroretinogram (mfERG) response density & latency; changes in best-corrected visual acuity (BCVA); safety outcomes; changes in mfERG & BCVA among participants on AREDS supplements and changes in microperimetry.	mfERG response density: in rings 1,2 & overall, but not in rings 3-6; no difference with AREDS supplements. mfERG latency: no difference in any of rings or overall; no difference with AREDS supplements. BCVA: 1.6 letters worse; no difference witj AREDS supplements. No saffron-related serious adverse events.	Saffron supplements: modest improvement of mfERG responses in AMD including those using AREDS supplements.
[42]	Norbixin (9'-cis-norbixin) from *Bixa orellana* seeds	To investigate the protective effects of norbixin against retinal damage in animal models of AMD & Stargardt disease.	***In vivo:*** BL-induced retinal damage in BALB/c mice & Abca4-/- Rdh8-/- DKO mice; immunohistochemistry; ERGs (kinetic analysis); histopathology & photoreceptor counting (Hoechst 33342); RPE counting (FE-SEM); A2E (HPLC-MS/MS); norbixin (HPLC).	Norbixin: protection of retina of BALB/c mice; reduction of the loss of scotopic a wave intensity; reduction in A2E accumulation; significant preservation of scotopic a, b waves & photopic b wave after 6 months.	Norbixin: optimal neuroprotection& maintenance of photoreceptor function& reduction of ocular A2E accumulation following chronic oral administration for 6 months in Abca4-/- Rdh8-/- mice.

[67]	Lutein (carotenoid)	To investigate the protective mechanism of lutein on RPE cells subjected to oxidative stress *in vitro*.	***In vitro:*** H_2O_2-induced oxidative stress in ARPE-19 cells; cell viability (MTT); caspase activities, ROS (DCFDA); cell cycle & apoptosis (flow cytometry); gene expression (qRT-PCR); protein expression (Western blot).	Lutein: increase of cell viability (dose-dependent); inhibition of the increased expression of total caspases (concentration-dependent); reduction of ROS; increase in transcription levels of inflammatory cytokines (IL-6, IL-8 & TNF-α); reduction in RPE cells in G_2/M phase; activation of CDK1 & CDC25C & decrease of cyclin B1.	Lutein: reversal of oxidative damage triggered G_2/M phase arrest of ARPE-19 cells, through the activation of cyclin-dependent kinase-1, cell division cycle 25C, & degradation of cyclin B1; potential effective anti-oxidant, which can be applied in the prevention of AMD, or other age-related diseases.
[52]	*Solanum lycopersicum* (Tomato) extract (rich in carotenoids)	To examine the uptake & protective potential of dietary carotenoids from tomatoes against retinal damage in RPE cells.	***In vitro:*** H_2O_2-induced oxidative stress in ARPE-19 cells; carotenoids (HPLC); nitrosative stress (fluorescence); protein carbonyls (ELISA); nitrotyrosine (immunocytochemistry); lipid peroxidation (MDA).	Tomato: marked reduction of nitrotyrosine formation; reduction of protein carbonylation & MDA formation. ARPE-19 cells: preferential accumulation of lutein & b-carotene rather than lycopene. Lutein uptake ratio: two-fold more significant than that of b-carotene & ten-fold more significant than that of lycopene.	Dietary tomatoes rich in carotenoids: protective effects against oxidative stress in the retinal pigment epithelium.
[80]	*Zeaxanthin (from colored fruits)*	To evaluate whether dietary supplementation with the carotenoid zeaxanthin raises macula pigment optical density (MPOD) & has unique visual benefits for patients with early AMD.	**Clinical trial:** RCT (n=60, 119 eyes) in early & moderate AMD patients: 8 mg zeaxanthin (n=25 subjects) vs. higher-dose 8-mg zeaxanthin/9-mg L combination (n=25) vs. Faux Placebo (9-mg L supplement control group (n=10). Central foveal 1° Macula Pigment Optical Density (MPOD); retinal image (fundoscopy); macular visual function test; foveal test (LogMAR acuity); parafoveal tests (flashed optotype, distance photopic contrast sensitivity function (CSF), photostress glare recovery test).	Zeaxanthin: increase of foveal MPOD in all 3 groups from low-normal to normal density by 18 months; improvement of near visual acuity; most efficient in improving the scotoma count; improvement of low-contrast letters & glare recovery when used in combination of either L or L plus zeaxanthin.	Zeanxanthin-induced foveal MPOD elevation mirrored that of L and provided complementary distinct visual benefits by improving foveal cone-based visual parameters, whereas L enhanced those parameters associated with gross detailed rod-based vision, with considerable overlap between the 2 carotenoids. The equally dosed (atypical dietary ratio) Zx plus L group fared worse in terms of raising MPOD, presumably because of duodenal, hepatic-lipoprotein or retinal carotenoid com-petition

Diaryheptanoids					
[74]	*Curcuma longa* L. extract (CLE) & its curcuminoids (Curcumin, Demethoxycurcumin & Bisdemethoxy-curcumin)	To investigate the protective effects of CLE & its curcuminoids against retinal damage *in vitro.*	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (LDH); gene expression (qRT-PCR).	CLE & curcuminoids: protective effects (dose-dependent); significant reversal of the increase in mRNA expression of c-Abl & p53; no significant change in mRNA expression of JNK1 & JNK2. Curcumin: a significant decrease in cell viability. Demethoxycurcumin & Bisdemethoxy- curcumin: significantly lower mRN44A expression of p38.	CLE & its curcuminoids: significant protection against photooxidative damage & apoptosis in RPE cells; highest activity with dimethoxy-curcumin.
[192]	Curcumin	To investigate the protective effects of curcumin anaog 1,5-bis (2-trifluoromethylphenyl)-1,4-pentadien-3-one (C3) against acrolein-induced ARPE-19 cell toxicity	***In vitro:*** Acrolein-induced ARPE-19 cells, exposed to curcumin & C3. Oxidative stress, GSH levels, mitochondrial function, gene transcription & translocation,	C3 & Curcumin: complete protection against oxidative stress & preservation of GSH levels & mitochondria function (C3: more potent); induction of Nrf2 nuclear translocation & Nrf2 target genes transcription (elimination by Nrf2 knockdown); activation of PI3/Akt pathway.	C3: promising drug candidate for eye diseases including AMD. Both: activation of phase II enzymes via direct disruption of Nrf2/Keap1 complex and promotion of Nrf2 nuclear translocation.
[193]	Curcumin	To screen the protective effects of candidate compounds including curcumin, against induced pluripotent stem cells (iPSCs) for macular degeneration.	***In vitro:*** iPSCs from patients with dry type AMD exposed to curcumin & candidate compounds. ROS production, gene expression (RT-PCR)	Curcumin: protection against oxidative stress of H2O2 through reduction of ROS, modulation of expression of oxidative stress-regulating genes (PDGF, VEGF, IGFBP-2, HO-1, SOD-2, GPX-1). RPE cells from AMD patients are more susceptible to oxidative stress, which leads to AMD.	Curcumin: ideal compound for AMD treatment.
[194]	*C. longa L.* & its curcuminoids	To investigate the protective effects of C. longa extract (CLE) & its curcuminoids against blue-light-inducted human RPE cell death	***In vitro:*** Blue light-induced AMD: human ARPE-19 cells exposed to CLE and its curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin). Cytotoxicity (LDH assay); gene expression (RT-PCR).	All: significant protective effects against blue light-induced cytotoxicity; reduction of mRNA levels of c-Abl & p53; inhibition of p38 expression (demethoxycurcumin, bisdemethoxycurcumin).	C. longa extract (CLE) & its curcuminoids: significant protection against photooxidative damage & apoptosis in RPE cells, potential for AMD treatment.
[195]	Prodrug of Curcumin: Curcumin diethyl disuccinate (CurDD), Curcumin	To investigate the protective effect of curcumin diethyl succinate (CurDD: prodrug of curcumin) compared with curcumin against H202-induced oxidative stress in human RPE cells.	***In vitro:*** H_20_2-induced AMD: human ARPE-19 cells exposed to CurDD or curcumin. Reactive oxygen species production, HO-1 & NQO1 gene expression.	CurDD & curcumin: a significant decrease in reactive oxygen species (ROS) production & protection against cell death (CurDD more active). Mechanism of action: modulation of p44/42 (ERK) & involvement of downstream Bx & Bcl-2; upregulation of HO-1 & NQO1 expression.	CurDD: more potent protective effect against oxidative stress-induced cell death than curcumin.
[196]	Curcumin metabolite: Hexahydrocurcumin (HHC)	To investigate the mechanism involved in the protective effect of hexahydrocurcumin (HHC: active metabolite of curcumin) in AMD.	***In vitro:*** Blue light-induced AMD: human ARPE-19 & mouse RPE cells exposed to HHC. Nect generation sequencing RNA sequencing.	HHC: promotion of autophagy by enhancing autophagic flux, reduction of oxidative stress & endoplasmic reticulum stress, and effective reversal of light-induced cell death.	HHC: protective effect against RPE cell death, beneficial for development of natural metabolite-based preventive drugs or functional foods.

Flavonoids					
[85]	Baicalin (a main effective flavonoid compound from *Srutellaria baicalensis*)	To investigate the protective effects of baicalin against pyroptosis-induced retinal damage in RPE cells.	***In vitro:*** Aβ-induced pyroptosis in ARPE-19 cells; cell viability (WST-8 & MTT); apoptosis & pyroptosis (flow cytometry); transfection; gene expression (qRT-PCR); protein expression (Western blot); miRNA binding site (dual luciferase reporter assay).	Baicalin: alleviation of pyroptosis; inhibition of pyroptosis via upregulating miR-223 while reducing pyroptosis markers (NLRP3, caspase-1 & ACS) & proinflammation cytokines (IL-1β & IL-18) expression. miR-223/NLRP3 axis: involvement in baicalin-mediated pyroptosis suppression in Aβ-induced ARPE-19 cells.	Baicalin: alleviation of intracellular pyroptosis & viability damage from Aβ inducement in human RPE cells via negative crosstalk of miR-223/NLRP3 inflammasome signaling.
[56]	Cynaroside (Cyn: a flavonoid glycoside)	To evaluate the protective effects of Cyn & its underlying mechanisms against retinal degeneration *in vitro & in vivo.*	***In vitro:*** A2E/BL-induced retinal degeneration in ARPE-19 cells; cell viability (MTT); apoptosis & autophagy (flow cytometry, caspase activity); ROS (DCFDA); cytokines (ELISA); protein localization (immunofluorescence). ***In vivo:*** A2E/BL-induced retinal degeneration in male SD rats (intravitreal); histopathology (ONL, INL& PL thickness; H&E); retinal image (fundoscopy); apoptosis (TUNEL); GSH, MDA levels & SOD activity (enzyme assay); protein expression (Western blot).	Cyn: protection against cell death (concentration-dependent); significant decrease of ROS production (concentration-dependent); decrease of MDA & increase of SOD & GSH levels (concentration-dependent)	Cyn: protective effects against A2E & BL-induced retinal degeneration by modulating autophagy & decreasing the NLRP3 inflammasome.
[34]	Glabridin (Glab: an isoflavane from the root extract of licorice)	To investigate the effect of Glab on the sodium iodate ($NaIO_3$)-induced retinal degeneration in vitro & in vivo.	***In vitro:*** NaIO3-induced retinal degeneration in ARPE-19 cells; cell viability (MTT, Hoechst 33342); apoptosis (flow cytometry); ROS (DCFDA); protein expression (Western blot).	Glab: no cytotoxicity; significant attenuation of cell death; reduction of late apoptotic cells; significant reduction of ROS production & phosphorylation of ERK1/2 & P38.	Glab: protection of RPE cells against oxidative stress & apoptosis by inhibiting phosphorylation of ERK1/2 & p38 MAPK pathway; significant prevention of retinal damage by stopping the progression of retinal degeneration & reducing the formation of deposits on the RPE layer induced by NaI03.
			In vivo: $NaIO_3$-induced retinal degeneration in C57BL/6J mice; ERG; histology (H&E); retinal image (OCT); protein expression (Western blot).	Glab: improvement of retinal function; significant increase in a- & b-wave amplitudes; significant reduction of retinal thickness; improvement of the arrangement of cells in ONL and PR layers; significant protection of the structure of the RPE layer by reducing the number of deposits.	

[26]	Myricetin, Quercetin & Kaempferol	To investigate the effect of flavonols - myricetin & structurally related quercetin & kaempferol against A2E & BL-induced photoreceptors death in bovine retinal cell culture.	***In vitro:*** Retinal section from bovine eyes - A2E (HPLC); cell death (fluorescence); apoptosis (immunocytochemistry); cell counting (automated imaging microscope).	Myricetin & Quercetin, but not kaempferol: inhibition of cell death (concentration-dependent). All: significant increase in the number of photoreceptors & bipolar cells.	Myricetin: prevention of A2E & BL-induced photoreceptors death in primary retinal cell cultures. Flavonols structurally related to myricetin: potential leads for the development of a new generation of molecules for clinical application in retinal diseases associated with photoreceptor cell death.
[88]	Puerarin (major active constituents of Kudzu root)	To investigate the protective effects including the underlying molecular mechanism of puerarin in RPE cells.	***In vitro:*** LPS/Aβ1-40-induced retinal damage in ARPE-19 cells; oligomerization; ROS (DCFDA); lipid peroxidation (spectrophotometer); ER stress (luminescence); protein expression (Western blot).	Puerarin: activation of Nrf2/HO-1 antioxidant signaling pathway; inhibition of Aβ1–40-induced phosphorylation of IRE1 & PERK, as well as nuclear expression of ATF6α.	Puerarin: protective effects on retinal damage by inhibition of NLRP3 inflammasome activation via suppressing oxidative stress & suppression of ER stress; potential for adjuvant treatment to reduce the inflammation of AMD.
[35]	Quercetin (found in plants, fruits, herbs, vegetables & nuts)	To investigate the anti-inflammatory effects of quercetin on cultured RPE monolayer cells & in the retinas of Ccl2-/- /Cx3cr1 -/- mice with oxidative stress & inflammation-related retinal degeneration.	***In vitro:*** A2E/BL-induced oxidative stress in ARPE-19 cells; cell viability (crystal violet); mitochondrial damage (MTT); apoptosis (comet assay); A2E (HPLC); COX activity (fluorescence); gene expression (qRT-PCR).	Quercetin: significant increase in cell viability & mitochondrial function; significant reduction of cellular apoptosis under oxidative stress induced by H_2O_2; reduction of BAX, FADD, CASPASE-3 and CASPASE-9 & enhancement of the transcription of BCL-2, BCL2/BAX ratio; inhibition of the transcription of TNF-a, COX-2 & INOS & slight suppression of COX production, but marked suppression of NO production.	Quercetin: protection of human RPE cells from oxidative stress in vitro via inhibition of pro-inflammatory molecules & direct inhibition of the intrinsic apoptosis pathway. Quercetin (25 mg/kg/d): no improvement of the retinal lesions in the knockout most likely due to insufficient suppression of ocular inflammatory & apoptotic pathways in the eyes.
			In vivo: H2O2-induced oxidative stress in Ccl2-/-/Cx3cr1 -/- DKO mice; fundoscopy; histopathology; gene expression (qRT-PCR); COX activity (fluorescence activity assay); PGE2 (PGE2 EIA kit) & NO (Griess colorimetric reaction); serum NADP+/NADPH (ECNP-100 assay kit).	Quercetin: no significant reduction in retinal lesions; no amelioration of retinal lesions; decrease of serum NO levels & slight decrease of NADP+/NADPH ratios; significant decrease in COX activity & PGE2 levels; no effect on the ocular transcription levels of Bcl-2 but inhibition of the increase in Bax & increase of Bcl-2/Bax ratio; no inhibition of the transcription of Fas, Fasl or caspase-3; no effective inhibition of the increase in the levels of Cox-2, iNOS & TNF-α transcription; reduction of ocular A2E levels.	

[63]	Quercetin-3-O-β-D-galactopyranoside (Hyperoside, a derivative of quercetin)	To investigate the protective effects & underlying molecular mechanisms of action of hyperoside against retinal damage in vitro & in vivo.	***In vitro:*** A2E/BL-induced ARPE-19 calls; cell viability (WST-8 & MTT); intracellular A2E (A2E-BDP fluorescence); luciferase assay (A549 cells); apoptosis (flow cytometry); ROS (DCFDA); complement activation (Western blot); protein expression (Western blot); gene expression (qRT-PCR).	Hyperoside: no cytotoxicity; effective inhibition of A2E accumulation (dose-dependent); inhibition of PMA-induced NF–κB & AP-1 activity (dose-dependent); significant recovery of C3 level; significant decrease of PARP cleavage; increase of AHR target genes expression CYP1A1 & CYP1B1.	Hyperoside: preventive effects through anti-oxidant activity, a potential application to prevent the onset and development of AMD.
			In vivo: BL-induced retinal damage in BALB/c mice; histopathology (H&E).	Hyperoside: protection against the decrease in thickness & loss of the number of nuclei (dose-dependent).	
[64]	Quercetin-3-O-α-L-arabinopyranoside (guaijaverin, a polyphenol fraction of *Vaccinium uliginosum*).	To investigate the protective effects of QA in retinal damage, including its underlying mechanism of action.	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (WST-8 &MTT); luciferase assay (A549 cells); gene expression (qRT-PCR); protein expression (Western blot); A2E (A2E-BDP fluorescence).	QA: no cytotoxicity; a significant decrease in A2E accumulation (dose-dependent); protection from apoptosis (dose-dependent) by suppression of PARP cleavage, NF-κB & AP1 activity, and activation of complement 3; increase in CYP1A1 & CYP1B1 gene expression; removal of intracellular A2E from cells (dose-dependent).	QA: most effective active compound from Vaccinium Uliginosum L. against BL-induced retinal damage both in *vitro & in vivo*, possibly through anti-inflammatory & anti-apoptotic activities.
			In vivo: BL-induced retinal damage in BALB/c mice; histopathology (H&E); caspase-3 (immunohistochemistry); protein expression (Western blot); apoptosis (flow cytometry).	QA: protection against the loss of retinal layers (dose-dependent); significant inhibition of caspase-3 expression; inhibition of inflammation & apoptosis through suppression of PARP-cleavage activity & activation of complement 3.	
[50]	Wogonin (from the root of *Scutellaria baicalensis)*	To investigate the protective effects & underlying molecular mechanisms of action of wogonin against retinal damage in RPE cells.	***In vitro:*** LPS-induced inflammation in ARPE-19 cells; paracellular permeability (TEER); gene expression (qRT-PCR); ZO-1 (immunofluorescence); cytokines (ELISA); protein expression (Western blot).	Wogonin: significant increase in TEER; significant reduction of tight junction proteins ZO-1 & claudin-1 expression; significant reduction of gene/protein expression of COX-2, iNOS, TNF-α, IL-1β, IL-6 & IL-8; significant decrease of NF-κB activation; significant reduction of TLR4 protein; inhibition of the activation of inflammation-associated cytokines through the TLR4/NF-κB pathway.	Wogonin: attenuation of the TLR4/NF-kB-mediated inflammatory response in LPS-stimulated ARPE-19 cells, and thus a potential therapy for treating AMD.
[60]	Quercetin-3-O-α-L-arabinopyranoside (QA)	To investigate the protective effects QA against retinal damage, including its underlying mechanism of action in vitro & in vivo.	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (CCK8); gene expression (RT-qPCR); protein expression (Western blot).	QA: no cytotoxicity; significant inhibition of oxidation of A2E (dose-dependent); inhibition of translocation of NF-κB & upregulations of inflammatory-related genes (IL-1β, IL-6, MCP-1, CXCL-2 &VEGF-A); inhibition of apoptosis by decreasing caspase 3 activation and PARP cleavage.	QA: protective effect against BL-induced retinal damage through anti-apoptosis and anti-inflammation both in vitro & in vivo.
			In vivo: BALB/cJ mice; histopathology (H&E); gene expression (qRT-PCR); protein expression (Western blot).	QA: restorage of the thicknesses of the whole retina, ONL, INL & PSL (dose-dependent; inhibition of apoptosis through decreasing caspase 3 activation and PARP cleavage.	

Iridoid glycoside					
[93] Iridoid glycoside	Genipin (GP) (an aglycone from the fruit of *Gardenia jasminoides)*	To investigate the effects & underlying molecular mechanisms of GP on RPE cells induced by H_2O_2.	***In vitro:*** H_2O_2-induced oxidative stress in ARPE-19 cells; cell viability (MTT); ROS (flow cytometry); apoptosis (flow cytometry); gene expression (qRT-PCR); protein expression (Western blot).	GP: reversal of inhibitory effects of H_2O_2 by promoting cell viability, attenuating ROS accumulation & cell apoptosis; increase of Nrf2, HO-1 & NQO-1 expression. Nrf2 silencing: enhancement of H_2O_2-induced damage to ARPE-19 cells. GP + siNrf2 vector: significant downregulation of the protein expression levels of Nrf2, NQO-1, HO-1 & Bcl-2, but significant upregulation of Bax & cleaved-caspase-3.	GP: attenuation of oxidative damage induced by H_2O_2 in ARPE-19 cells. Nrf2 silencing: attenuation of the protective effects of GP on H_2O_2-induced ARPE-19 cells.
Phenolic acid					
[84]	*Ribes nigrum L. (*blackcurrant) extract	To investigate the protective effects and underlying molecular mechanisms of action of *R. nigrum* against retinal damage *in vitro & in vivo.*	***In vitro:*** BL-induced retinal damage in ARPE-19 cells; cell viability (WST-8); ROS (DCFDA); gene expression (qRT-PCR); A2E (A2E-BDP fluorescence). ***In vivo:*** A2E/BL-induced retinal damage BALB/c mice; histopathology (H&E); retinal image (ophthalmological examination); SOD-1 (immunohistochemistry).	BCE: no significant cytotoxicity; significant inhibition of cell death; significant decrease of ROS levels (concentration-dependent); significant downregulation of the expression of genes induced by A2E & BL.	BCE: preventive & therapeutic effects on dry AMD through antioxidant activity & inhibitory activity of lipofuscin accumulation in the retina.
Protein					
[53]	*Spirulina maxima* extract	To investigate the protective effects including its underlying mechanisms of action of *S. maxima* against retinal damage *in vitro & in vivo.*	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; **c**ell viability (WST-8)**;** ROS (DCFDA); gene expression (qRT-PCR); protein expression (Western blot); chemical analysis (HPLC).	*S. maxima*: no cytotoxicity; inhibition of cell death; a significant decrease in total ROS/RNS level (concentration-dependent); regulation of inflammatory response (NF-κB, CXCL-2, IL-1β, IL-6 & MCP-1). P-phycocyanin: main active compound of *S. maxima* in RPE cells.	*S. maxima*: anti-apoptotic effects through modulating NF-κB pathway in RPE cells; restorage of retinal layer thickness & suppression of the expressions of angiogenesis-related genes in the mouse retina.
			In vivo: A2E/BL-induced retinal damage in BALB/c mice; histopathology (H&E); ONL; INL; PL; whole retina; gene expression (qRT-PCR); protein expression (Western blot).	*S. maxima: p*rotection of photoreceptor degeneration (increase in thicknesses); inhibition of ROS production *via* regulating NF-κB pathway, inflammation-related genes expression & apoptosis (*Bax/Bcl-2*). Inhibition of the expression of angiogenesis-related genes (MMP-2, MMP-9 & VEGF-A).	

Polyphenols					
[70]	Lipophenols (alkyl-(poly)phenol derivatives: Phloroglucinol, Resveratrol, Catechin & Quercetin as the main backbone)	To perform a rational design of different families of lipophenols to conserve anticarbonyl stress activities & improve their antioxidant properties.	**Chemical synthesis & Characterization:** NMR; HRMS analysis; Rf & melting point A2E & BL-induced epithelial degeneration in ARPE-19 cells; cell viability (MTT); ROS (DCFDA).	Confirmation of anti-COS (carbonyl & oxidative stress) of most quercetin lipophenols. C-phloroglucinol derivatives: P-OiP-OLA (LEAD A), P-OiP-ODHA (LEAD B), P-OiP-CLA (8a), P-OiP-CDHA (8b). Resveratrol analogues: alkyl resveratrol-PUFA (15a/15b), an isopropyl-resveratrol derivative not linked to PUFA (R-5OiP (13)), derivatives related to PUFAs without alkyl function named resveratrol-4′ LA (R-4′ LA) & resveratrol-4′ DHA (R-4′ DHA). Flavonoid lipophenol analogues, Catechin lipophenols; alkyl-catechin derivatives C-7OiP (18a) & C-5OiP (18b), alkyl-lipophenol derivatives C-3LA-7OiP (19a) & C-3LA-5OiP (19b), Quercetin-5OiP lipophenols; Q-3LA-5OiP (29), PUFA-free analogue Q- 5OiP (23), Quercetin-7OiP lipophenols, alkyl quercetin Q-7OiP (35), lipophenol derivatives Q-3LA-7OiP (39a), Q-3DHA-7OiP (39b).	Q-3DHA-7OiP (quercetin lipophenol): optimal DHA-quercetin; anti-COS lipophenol with optimized anti-oxidant properties; high protection against retinal toxicity; the most powerful lipophenol to suppress photo-oxidative toxicity initiated in RPE cells by A2E.
[89]	Quercetin & Chlorogenic acid (a phenolic compound widely found in fruits & vegetables, *e.g.* apples, pears, carrots, tomatoes, and sweet potatoes & in coffee & tea.	To investigate the protective effects of quercetin & chlorogenic acid against retinal damage in pigmented rabbits.	***In vivo:*** BL-induced retinal damage in pigmented rabbits; inflammatory markers (ELISA); apoptosis (flow cytometry); gene expression (qRT-PCR); protein expression (Western blot); histopathology (H&E).	Quercetin & Chlorogenic acid: inhibition of oxidative stress & inflammation; upregulation of HO-1 expression; inhibition of apoptosis through inhibition of Bax & activation of Bcl-2 expression; significant reduction of VEGF & HIF-1α expression; prevention of the reduction of ONL thickness.	Quercetin & Chlorogenic acid: protective effects on retinal degeneration through antioxidant & antiapoptotic activities, including anti-angiogenesis activity. Dietary polyphenols: novel strategies to prevent the onset & development of AMD.
[71]	Resveratrol, Quercetin, Phloroglucinol, Catechin & their derivatives	To synthesize novel lipophenol derivatives starting from known antioxidants (resveratrol, phloroglucinol, quercetin & catechin). To investigate the protective effects of the polyunsaturated lipid chain on their capacity to maintain ROS scavenging properties in RPE cells.	Synthesis of PUFA Lipophenols (HR-MS; NMR; UV spectroscopy) ***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (MTT); ROS (DCFDA).	All phloroglucinol & resveratrol: no cytotoxicity. Natural catechin: no apparent cytotoxicity, but its lipid derivatives have slight cytotoxicity at high concentrations. Quer-3-ALA: high toxicity. ROS inhibition of phloroglucinol-lipophenol & resveratrol-4′-LA: lower than its natural analogue. ROS inhibition of catechin analogues: similar potency with natural catechin. Quer-7-ALA: best antioxidant activity. Quer-3-LA & Quer-7-ALA: protective effects against cell death (concentration-dependent)	Quercetin conjugated to linoleic or α-linolenic acid: promising lipophilic antioxidants, protecting ARPE-19 cells from A2E-induced cell death more effectively than the parent polyphenol, quercetin.

[91]	*Vaccinium uliginosum* L. extract & its fractions	To investigate the protective effects & underlying molecular mechanisms of action of *V. uliginosum* extract & its fractions against retinal damage in RPE cells.	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (spectrophotometer); A2E (HPLC); FAB-MS; protein expression (Western blot).	Polyphenol & Anthocyanin: significant rescue cell death (dose-dependent). *V. uliginosum* & fractions (except sugar/acid fraction): prevention of cell death; inhibition of A2E accumulation & photo-oxidation. *V. uliginosum*, Polyphenol & Anthocyanin: effective inhibition of oxidation of A2E. Polyphenol compounds (myricetin-3-O-galactoside, quercetin-3-O-galatoside, quercetin-3-O-arabi- nofuranoside, myricetin & quercetin): increase of cell viability. *V. uliginosum* & quercetin-3-O-arabinofuranoside: decrease of cleaved caspase-3 & Bax/Bcl-2 expression.	*V. uliginosum*: significant reduction of blue light-induced ARPE-19 cell death; supplementation could exert beneficial effects on AMD.
[65]	*Vaccinium uliginosum* L. fractions	To investigate the preventive effects of *V. uliginosum* fractions containing polyphenol components against retinal damage *in vitro & in vivo.*	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells: cell viability (MTT); A2E-photooxidation (spectrophotometry).	VE, FE & FH (FE, EtOH eluted fraction; FH, fraction using HP20 resin; VE, VU water extract): no cytotoxicity; rescue from cell death; effective inhibition of intracellular A2E accumulation & A2E oxidation–mediated effects on cell death (dose-dependent). FHs: active fractions with higher polyphenol contents than the others. Isolated compounds: Quercetin, Hyperoside (Quercetin-3-O-β-D-galactopyranoside), Quercetin-3-O-α-L-arabinopyranoside, Cyanidin-3-O-β-D-glucopyranoside, Myricetin, Myricetin-3-O-β-D-galactopyranoside, Syringetin-3- O-β-D-galactopyranoside, Methylchlorogenate, Chlorogenic acid, Loganic acid & 6,7 Dihydromonotropein methyl ester (splendoside).	*V. uliginosum*: protection of retinal cells against BL-induced photoreceptor degeneration both *in vitro & in vivo.* Fractions of *V. uliginosum*: potential for development as a food or supplement to delay the onset or control retinal diseases.
			In vivo: A2E/BL-induced retinal damage in male BALB/c mice; histopathology (H&E)	*V. uliginosum* fractions: prevention of the degeneration of ONL nuclei & decrease of photic damage.	
[59]	*Vaccinium uliginosum* L. polyphenol-enriched fraction	To investigate the protective effects & underlying mechanisms of action of *V. uliginosum* polyphenol-enriched fraction against retinal damage in RPE cells.	***In vitro:*** A2E & BL-induced retinal damage in ARPE-19 cells; cell viability (MTT); gene expression (qRT-PCR; mRNA sequencing & pathway analysis); luciferase assay (A549 cells); ROS (DCFDA); complement activation & protein expression (Western blot); A2E accumulation (A2E-BDP fluorescence).	*V. uliginosum* polyphenol-enriched fraction: protective effect against cell death; no cytotoxicity; inhibition of inflammatory signaling (TNF-α signaling pathway, AP- 1 pathway & complement activation); significant decrease in RASD1 expression; significant reduction in the levels of cleaved PARP; inhibition of accumulation of A2E; effective removal of A2E (dose-dependent).	*V. uliginosum* polyphenol-enriched fraction: protective effects against retinal damage through modulation of TNF-α signaling pathway, AP- 1 pathway & complement activation.

[61]	*Arctium lappa* L. extract (ALE)	To investigate the protective effects of ALE on dry AMD models, including A2E-induced damage in ARPE-19 cells & *in vivo* light-induced retinal damage in BALB/c mice.	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells –phenolic (Folin-Ciocalteu method) & flavonoid (Aluminum chloride colorimetric method); ROS (DCFDA); cell viability (WST-8 & MTT); A2E (HPLC); antioxidant activity (DPPH, ABTS, FRAP); protein expression (Western blot).	ALE: significant increase of both total phenolic content & total flavonoid contents (dose-dependent); no cytotoxicity; attenuation of A2E accumulation (concentration-dependent); inhibition of apoptotic signaling pathway by downregulating Bax & cleavage of caspase-3 & upregulation of Bcl-2; suppression of ROS level (dose-dependent).	ALE: protection of human ARPE-19 cells & BALB/c mice from A2E- & light-induced damage and cell death, through suppressing ROS-induced cell apoptosis.
			In vivo: Light exposure in BALB/c male mice - histology (H&E)	Light: damage to retinal ALE, leutien: significantly inhibited light-induced retinal damage (dose-dependent).	ALE: protection of the outer nuclear layer in retina against light-induced AMD.
Saponins					
[24]	*Centella asiatica* extract (CA-HE50) & Asiaticoside	To investigate the cytoprotective effects & underlying mechanisms of CA-HE50 & asiaticoside in ARPE-19 cells & C57BL/6 mouse macular tissues.	***In vitro:*** N-methyl-N-nitrosourea (MNU)-induced retinal damage in ARPE-19 cells; CA-HE50 (HPLC); cell viability (MTT assay); protein expression (Western blot); cell cycle analysis (Tali-based cytometer); histopathology (H&E).	CA-HE50: increase of cell viability (concentration-dependent); inhibition of apoptosis through increasing the pro-caspase-3 and 9 & cell cycle regulation (S phase arrest); activation of Nrf2/HO-1 antioxidation pathway; inhibition of A2E accumulation.	CA-HE50: prevention of AMD progression through inhibition of the intrinsic apoptosis pathway & prevention of cell cycle arrest caused by activation of Nrf2/HO-1 signaling pathway; strong anti-oxidant effect due to asiaticoside.
			In vivo: MNU-induced retinal degeneration in C57BL/6; histology (H&E); protein expression (Western blot).	CA-HE50: significant increase in the thickness of ocular tissue (dose-dependent). MNU: significant thinner of ocular tissue thinner of ocular tissue.	
[54]	*Panax ginseng* berry (*Panax ginseng* Meyer) Ginseng berry extract (GBE)	To investigate the protective effects of GBE & its underlying molecular mechanisms on retinal damage *in vitro & in vivo.*	***In vitro:*** A2E/blue light (BL)-induced retinal damage in ARPE-19 cells; cell viability (WST-8); ROS (DCFDA); gene expression (qRT-PCR); protein expression (Western blot).	GBE: no cytotoxicity; inhibition of cell death (concentration-dependent); activation of SIRT1/PGC-1α signaling pathway regulating NF-$_k$B translocation, caspase-3 activation, PARP cleavage, expressions of apoptosis-related factors (Bax/Bcl-2, LC3-II, p62) & ROS production); inhibition of inflammation; inhibition of apoptosis by regulating caspase 3 activation, PARP cleavage & restorage of the inhibition of autophagic flux. Ginsenoside Re (active component of GBE): no cytotoxicity; suppression of BL-induced cell death (concentration-dependent).	GBE: prevention of retinal cell death through inhibition of inflammation *via* SIRT1/PGC-1a & NF-$_k$B pathways & suppression of apoptosis by regulating caspase-3 activation, PARP cleavage & autophagic flux.
			In vivo: BL-induced retinal damage in BALB/c male mice; histopathology; ONL; IN; PL; whole retina (H&E); gene expression (qRT-PCR); protein expression (Western blot); chemical analysis (UHPLC-ESI-MS/MS).	GBE: protection against retinal degeneration; activation of SIRT1/PGC-1α signaling pathway; inhibition of apoptosis by regulating caspase 3 activation, PARP cleavage & restorage of the inhibition of autophagic flux; protection of retinal layers by restoring their thickness.	

Stilbenoids					
[68]	Piceatannol (a metabolite of resveratrol found in red wine, grapes, passion fruit, white tea & Japanese knotweed)	To investigate the protective effects against retinal damage, including underlying mechanisms of action of piceatannol in RPE cells.	***In vitro:*** H_2O_2-induced retinal damage in ARPE-19 cells; cell viability (WST-8); apoptosis (flow cytometry); siRNA targeting human Nrf2; protein expression (Western blot); gene expression (qRT-PCR); ROS (dihydroethidium; flow cytometry).	Piceatannol: inhibition of apoptosis (dose-dependent); reduction of intracellular ROS (dose-dependent); induction of Nrf2 signaling activation [increase of transcription of antioxidant genes SD, HO-1 & glutamate-cysteine ligase catalytic subunit (GCLc)].	Piceatannol: protection of ARPE-19 cells against photo-oxidative damage & oxidative stress through activation of PI3K/Akt signaling. Piceatannol & grape extracts rich in piceatannol: the potential to reduce the risk of age-related retinal degenerative disease.
[48]	Resveratrol	To investigate the protective effects of resveratrol against retinal damage, including its underlying mechanism of action *in vitro.*	**Chemical characterization:** NMR ***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (CV, MTT); apoptosis (DAPI); ROS (DCFDA); cell monolayer formation (TEER); cell permeability (FITC); mitochondrial morphology (MitoTracker Red CMXRos); antioxidant activities (CAT, SOD)	Resveratrol: no cytotoxicity up to 100 μM; prevention of A2E-induced toxicity; decrease in apoptotic cell death; protection of junctional integrity of cells; reduction of ROS level both intracellular & mitochondria; promotion of anti-oxidant activity by increasing CAT & SOD level; reduction of mitochondrial fragmentation.	Resveratrol: protection against A2E-induced toxicity effects in ARPE-19 cells through decreasing apoptotic cells & ROS level; protection of RPE monolayer integrity.
[22]	Resveratrol (a polyphenol found in plants, *e.g.*, red wine, grapes, some berries & peanuts) & its analogs Piceatannol & Resveratrol glycones	To investigate the protective effect of resveratrol, piceatannol & resveratrol glycones against retinal damage in RPE cells.	***In vitro:*** A2E/BL-induced cell death in ARPE-19 cells; cell viability (MTT); A2E oxidation products (FAB-MS); A2E (protein assay).	Resveratrol & Piceatannol alone: no significant cytotoxic effects; increase in cell viability (dose-dependent); strong inhibitory effect on A2E photo-oxidation; inhibitory effect of A2E accumulation. Piceatannol: slightly more protective effect of A2E photo-oxidation. Resveratrol glycone: partial protective actions (RES-3,40-O-b-D-diglucoside: most effective).	Resveratrol & its analogs: protective effects against ARPE-19 cells from A2E & BL-induced cell death through regulation of A2E accumulation as well as photooxidation of A2E, a beneficial effect for AMD treatment.
Terpenoids					
[51]	Betulinic acid & its derivatives (triterpenoids extracted from the bark of birch trees)	To investigate the protective effects of betulinic acid, betulin & their derivatives on hypoxia-induced oxidative stress in human RPE cells.	***In vitro:*** Cobalt chloride-induced hypoxia stress in ARPE-19 cells; cell viability assay (MTT); ROS (DCFDA); apoptosis (flow cytometry); protein expression (Western blot).	3-O-acetyl-glycyl- 28-O-glycyl-betulinic acid (H7): significant attenuation of cytotoxicity, oxidative stress, apoptosis & necrosis; inhibition of the activation of *Akt*, *Erk* & *JNK*. Compounds H1, H11 & H14: mild cytotoxicity. Compounds H2, H4, H6, H9 & H19: moderate cytotoxicity.	3-O-acetyl-glycyl- 28-O-glycyl-betulinic acid (H7): safe & effective in protecting RPE cells from cobalt chloride-induced hypoxia stress; significant improvement of cell viability through decreasing cellular ROS; attenuation of the activation of Akt, ERK & JNK signaling.

[62]	*Prunella vulgaris var. lilacina* extract	To investigate the protective effects & its underlying molecular mechanisms of action of *Prunella vulagris* extract on RPE cell damage *in vitro & in vivo.*	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells; cell viability (WST-8); A2E (HPLC); total ROS/RNS, MDA, GSH, SOD & VEGF (ELISA); gene expression (qRT-PCR); protein expression (Western blot).	*P. vulgaris*: no cytotoxicity; inhibition of cell death & intracellular A2E accumulation (dose-dependent); inhibition of ROS-mediated apoptosis; activation of Nrf2/HO-1 signaling pathway & inflammation.	*P. vulgaris*: protective effects against retinal damage by anti-oxidant effect through activating Nrf2/HO-1 pathway in early stage & inhibiting NF-kB translocation in late stage; inhibition of the onset & development of AMD simultaneously.
			In vivo: BALB/c male mice (4 days & 14 days treatment); histopathology (H&E); ONL, IN, PL & whole retina (optical microscope); localization (immunohistochemistry); MDA, GSH, SOD (ELISA); gene expression (qRT-PCR); protein expression (Western blot).	*P. vulgaris* extract: inhibition of BL-induced retinal degeneration & inflammation.	
[71]	RS9 (triterpenoid, an Nrf2-specific activator)	To investigate the effect of RS9 against retinal damage model both *in vitro* & *in vivo*	***In vitro:*** NaIO3-induced retinal degeneration in ARPE-19 cells; cell viability (CCK8); cell death assay (Hoechst 33342); mitochondrial membrane potential assay (JC-1); protein expression (western blot); immunostaining; transfection	RS9: increase of cell viability (dose-dependent); increase of cell death (HO-1); increase of autophagic flux (LC3-II/LC3-I, LC3-autophagosome & SQSTM1).	RS9: protective effect against retinal degenerative through antiautophagic activity.
			In vivo: Light-induced retinal damage (LIRD) in wild-type zebrafish (intravitreal injection); histochemistry (Hoechst 33342)	RS9: suppression of the thinning of ONL thickness; increase of ONL.	
Mixed groups					
[17]	Vitamins E & C, Butylated hydroxytoluene, Resveratrol (Stilbenoid), a trolox analogue, Bilberry (*Vaccinium myrtillus*, polyphenol*)* extract, Ginkgolide B (from *Ginkgo biloba*, sapoin)	To determine the effect of epoxidized A2E on DNA damage. To evaluate the protective effects of various antioxidants (vitamins E & C, butylated hydroxytoluene, resveratrol, bilberry & ginkgolide B in A2E-epoxides-induced macular degeneration model *in vitro.*	***In vitro:*** light-induced retinal damage in ARPE-19 cells; A2E (HPLC, FAB-MS); DNA damage (comet assay); 8-Oxodeoxyguanosine (immunostaining); cell viability (DAPI).	A2E-epoxides: induction of cellular damage. Vitamins E & C: protection against DNA damage; reduction of A2E epoxidation. Vitamin E: protection against A2E-epoxidation by quenching singlet oxygen (more effective than vitamin C). Butylated hydroxytoluene, Resveratrol, PNU-83836E, Bilberry: inhibition of epoxidation of A2E. Ginkgolide B: small effect in reducing A2E-epoxidation.	Antioxidants such as vitamins E & C, butylated hydroxytoluene, resveratrol, a trolox analogue & bilberry extract: reduction of A2E-epoxidation and subsequent DNA damage & cell death.
[49]	Lutein (carotinoid) & Zeaxanthin (anthocyanin)	To evaluate the protective effects of lutein & zeaxanthin supplementation against photo-oxidative damage to RPE & oxidation-induced changes in the expression of inflammation-related genes.	***In vitro:*** A2E/BL-induced photooxidative damage in ARPE-19 cells; MCP-1, IL-8 & CFH (ELISA); gene expression (qRT-PCR); protein expression (Western blot); lutein & zeaxanthin (HPLC); proteasome activity (enzyme assay).	Lutein & Zeaxanthin: significant attenuation of photooxidation-induced accumulation of ubiquitin- proteins conjugates; decrease of MCP-1 & IL-8 expression; partial prevention of decreased CFH expression.	Lutein & Zeaxanthin: modulation of inflammatory responses in RPE cells in response to photo-oxidation (protecting the proteasome from oxidative damage).

[75]	Lutein (carotenoid) & Zeaxanthin (anthocyanin)	To investigate the photo-protective effects of lutein & zeaxanthin in Taiwanese subjects with early-stage AMD.	***Clinical:*** RCT in middle-aged Taiwanese subjects with early-stage AMD (n=56); serum lutein & zeaxanthin (HPLC); plasma oxidative index (chemiluminescence); antioxidant enzymes in RBCs (Biuret reaction); anti-inflammatory markers (ELISA); best-corrected visual acuity (ophthalmic examination).	Lutein: marked reduction of total free radicals & TBARS levels; increase of glutathione content & anti-oxidant enzymes (SOD, CAT & Gpx) levels; marked reduction of hs-CRP level; no significant alterations in IL-8 & fibrinogen; marked elevation in OCI & MPOD levels; marked reduction of BCVA, IOP & PSR levels.	Daily supplementation with lutein: remarked anti-oxidant enzyme activity & plasma total antioxidant capacity.

Table 2 Non-herbs molecules which have been investigated for their potential protective activities against AMD.

Ref	Compound/Extract	Objectives	Study models & Methodology	Main findings	Conclusions
Biological compounds					
[55]	Docosahexaenoic acid (DHA: unsaturated fatty acids)	To investigate the preventive effect of dietary DHA on age-related functional losses & A2E accumulation in a transgenic mouse model.	***In vivo:*** E4 transgenic (line TG2) mice; ERG; DHA (GC); A2E (HPLC); protein localization (immunohistochemistry).	DHA: no effect on morphology or number of photoreceptors; increase of DHA/AA ratios; a significant increase in plasma DHA; no change in ERG responsiveness & no preservation of a- or b-wave amplitudes but preventative effect on the declining c-wave 1-6 months of supplementation; increase in amplitude of a- and b-waves 12-18 months; marked reduction of A2E.	DHA supplementation: preservation of retina function at mid-degenerative stages in E4 mice, the potential of broad preventative therapeutic applications for age-related ocular diseases.
[87]	Docosahexaenoic acid (DHA) & Lutein-enriched eggs	To examine whether the consumption of lutein & DHA-enriched eggs can improve visual function among older adults at risk of AMD.	**Clinical study:** (n=30): Healthy Caucasian >50 yr (n=30); ERG; questionnaire; food record; plasma & egg lutein content (GC); plasma, RBC & egg fatty acids (GC); lipid profiles & lipoprotein subfractions (polyacrylamide gel electrophoresis).	DHA & lutein-enriched eggs: improvement of retina function & photopic b-wave maximum amplitude; increase of scotopic a-wave maximum amplitude; no adverse effect on blood lipid parameters. DHA concentrations: significant increase from pre- to during and maintained into post-assessment.	DHA-enriched eggs (daily for 6 wk): improvement of rod photoreceptor & cone-driven inner retinal cell responses in healthy Caucasian older adults; requirement of optimal maintenance & functioning of the retina.
[38]	Omega-3 fatty acid (rich in EPA & DHA) in pelleted diets with high conent	To evaluate the effect of a high omega-3 fatty acid diet on the retinas of *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO mouse model of AMD.	***In vivo:*** *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO & WT C57BL/6 mice – fundoscopy; histopathology (H&E, TEM), A2E (LC/MS/MS); PGs (ELISA); gene expression (qRT-PCR).	Pelleted diets with high omega-3 fatty acid: slow progression of retinal lesions; decrease in pro-inflammatory cytokines (PGE_1, LTB_4, TNF-α & IL-6) & increase of anti-inflammatory cytokines (PGD_2).	A diet enriched in EPA & DHA: amelioration of the progress of retinal lesions, possibly via shunted arachidonic acid pathway, leading to an increase of an-inflammatory derivatives such as PGD_2 & a decrease of pro-inflammatory derivatives such as PGE_2, LTB_4, TNF-α & IL-6.
[82]	Phosphatidylglycerol (PG)	To evaluate protective effect of PG against retinal damage in *vitro & in vivo.*	***In vitro:*** A2E/BL-induced photo-oxidation in primary human RPE cells; apoptosis (avexinV-FITC/PI, Hoechst-33342); oxidative & nitrosative stress (DCFDA) ***In vivo/Ex vivo:*** Wistar rats; liver mitochondria isolation; mitochondrial H_2O_2; glutathione activity (HPLC)	PG: protection of apoptotic cell death from A2E-induced photo-oxidation (dose-dependent). A2E: increase of H_2O_2 in mitochondria; GSH shift to GSSH in mitochondria.	PG: potent inhibition of apoptosis from A2E-induced oxidative stress.

Chemical compunds					
[57]	All-*trans*-retinylamine (Ret-NH2, visual cycle inhibitor) & others visual cycle inhibitors (farnesylamine, fenretinide, TDH, TDT, 13-cis-RA, and all-trans-RA)	To compare therapeutic potential of retinoid cycle inhibitors against retinal degenerative diseases *in vitro* & *in vivo.*	***In vitro:*** LRAT/RDH transduced-NIH3T3 cells; isomerization (HPLC); retinoid uptake (HPLC).	Ret-NH2 & farnesylamine: greatest inhibitory effects. Ret-NH2: most potent inhibitor (IC_{50}= 650 nM); inhibition of visual cycle > 18 h.	Ret-NH2: the most potent & specific inhibitors of the visual cycle.
			In vivo: Rbp-/- mice (intraperitoneal injection); liver Ret-NH_2 & N-retinylamides (HPLC); A2E (HPLC); ERG.	Ret-NH2: no toxicity in mice at effective dose (farnesylamine significant toxicity); reduction of A2E & iso-A2E generation; not depending on RBP/STRA6 mechanism; sustained ERG response (after bleaching 16 h)	
[32]	CU239 (a novel RPE65 inhibitor which is a key enzyme in the visual cycle)	To evaluate the effects of the non-retinoid compound CU239 on suppression of visual cycle & prevision of retinal degeneration in silico, in vitro & in vivo.	***In silico:*** screening of potential bovine RPE65 (PDB ID: 3KVC) inhibitors (QFIT score)	CU239: most inhibitory activity on RPE65 isomerase (IC50 = 6 μM).	CU239: a novel non-retinoid compound; a specific & potent inhibitor of RPE65 (direct competition with substrate all-trans-retinyl ester); useful for studies on the catalytic mechanisms of RPE65 & development of a potential approach to offset the retinoids imbalance caused by a defective visual cycle.
			In vitro: Bovine RPE microsome; retinol isomerase activity (HPLC); RPE65 fluorescence binding assay.	CU239: marked reduction of 11-cis-ROL; no change in LRAT; a competitive inhibitor of RPE65.	
			In vivo: Light-induced retinal damage in BALB/cJ mice homozygous for Rpe65-Leu450 polymorphism; histopathology (H&E); retinoid profile (HPLC); ERG.	CU239: inhibition of chromophore regeneration (dose-dependent); a significant decrease in 11-cis-RAL regeneration; increase in all-trans-retinyl ester (substrate of RPE65); mild reduction of ONL thickness; a significant increase of visual sensitivities.	
[81]	Emixustat hydrochloride	To determine whether emixustat reduces the rate of enlargement of geographic atrophy (GA) in subjects with AMD. To evaluate the safety & tolerability of emixustat over 24 months of treatment.	***Phase 2b/3 clinical trial (n=503):*** multicenter, randomized, double-masked, placebo-controlled (49 sites in USA, 7 sites in Germany); FAF & IOP (Heidelberg Spectralis devices); retinal image (Color fundus photography); best-corrected visual acuity (NL-BCVA & LL-BCVA); visual acuity (total letter score); RPE atrophy (SD OCT); GA lesion.	Subjects with a larger low luminance deficit (LLD) at baseline: more rapid growth of GA over 24 months. No relationship between the risk-allele status of the AMD-associated single-nucleotide polymorphisms. Most common adverse events: delayed dark adaptation (55%), chromatopsia (18%), visual impairment (15%) & erythropsia (15%)	Emixustat: no reduction of the growth rate of GA in AMD.

[78]	Hydrogen sulfide (H_2S)	To investigate the modulatory effects of endogenous & exogenous H_2S in homocysteine (Hcy)-induced inflammation in ARPE-19 cells.	***In vitro*** NaHS/Hcy -induced inflammation in ARPE-19 cells; cell viability (MTT); homocysteine uptake (ATBO+, RFT1); ROS (DCFDA); extracellular H_2S estimation (free radical H_2S analyzer); gene expression (qRT-PCR); cytokines (ELISA); protein expression (Western blot); cystathionineβ-synthase (immunofluorescence).	NaHS: blockage of hydrogen sulfide release & downregulation of mRNA & protein levels of IL-6 & IL-8. Hcy: no induction of cell death; increase in ATBO+ expression & decrease in RTF1 expression, indicating uptake inside the cells; significant increase (30 μM) of CBS but not CSE mRNA expression (trans-sulfuration pathway); increase of extracellular H2S, IL-6 & IL-8.	Exogenous supply of hydrogen sulfide either by NaHS or Compound 1c: anti-inflammatory effects in Hcy-induced inflammation in RPE cells.
[86]	2-(2-Hydroxyethoxy) ethyl (HEE) carbamate-modified acid-labile PRX (HEE-PRX)	To elucidate the contribution of the intracellular dissociation of PRXs to release threaded β-CDs on the excretion of A2E in vitro.	***pH-dependent dissociation of HEE-PRX (size exclusion chromatography: SEC)***	N-Trt stopper molecules from HEE-PRX: stimulation of dissociation of the PRX structure & the release of HEE-β-CDs.	EE-PRXs: promising candidates for the treatment of macular diseases through the removal of toxic metabolites. Comparative studies between acid-labile vs. nonlabile PRXs: essential insights into the design of supramolecular therapeutic agents and the potential efficacy of acid-labile PRXs for treating AMD.
			In vitro: A2E/BL-induced retinal damage in ARPE-19 cells; cellular uptake (flow cytometer & confocal microscope); intracellular triphenylmethanol (GC-MS); inclusion complex formation with retinol; A2E (HPLC); A2E toxicity & phototoxicity (WST-8).	HEE-PRXs: localization in endosomes & lysosomes; no cytotoxicity; immediate dissociation after cellular internalization to release threaded HEE-β-CDs (time-dependent); reduction of the number of A2E- positive puncta; attenuation of phototoxicity of A2E, probably due to effective removal of A2E from the cells. Acid-induced release of threaded HEE-β-CDs: solubilization of retinol through inclusion complexation.	
[90]	Lipoxin A4 (LXA4)	To examine the protective effects & underlying molecular mechanisms of action of LXA4 on retinal damage (oxidative-stress injury) in vitro & in vivo.	***In vitro:*** A2E/BL-induced ARPE-19 cells; cell viability (WST-1); ROS (dihydroethidium); apoptosis (flow cytometry); protein localization (immunofluorescence); protein binding (EMSA); protein expression (immunoprecipitation & Western blot).	LXA4: inhibition of BL-induced reactive ROS production; reduction of tight junctions & death of A2E-laden RPE cells; potent increase in expression of HO-1 & NQOI-1 by decreasing the association between Nrf2 & Keap1; amelioration of Nrf2 nuclear translocation & antioxidant response element (ARE) - DNA binding activity.	LXA4: prevention of oxidative damage of RPE cells through oxidative stress amelioration & antioxidant system activation (Nrf2/ARE signaling pathway).
			In vivo: LXA4/Aspirin & BL-induced retinal damage in BALB/c male mice; retinal imaging (OCT); histopathology (H&E); protein localization; (immunofluorescence).	LXA4: significant amelioration of retinal damage evidenced by reduction of thicknesses of the retinal layers & tight junctions of RPE cells.	LXA4: amelioration of retinal degeneration.

[92]	3-methyladenine (3-MA, an autophagic inhibitor) & rapamycin (an autophagic activator)	To examine the role of autophagy in the RPE cells & protective effects of 3-MA & rapamycin against retinal damage in vitro.	***In vitro:*** A2E-induced ARPE-19 cells; cell viability (CCK8); cell morphology (TEM); protein expression (Western blot); cytokines (Procarta cytokine profiling kit); immunofluorescence.	3-MA: no significant cytotoxicity; inhibition of A2E-induced autophagy through reducing autophagosome (LC3, LC3-II & beclin-1); increase of inflammatory factor levels (IL-1β, IL-2, IL-6, IL-8, ICAM, IL-17A, IL-22, MCP-1 & SDF-1); increase of angiogenic cytokine level (VEGFA). Rapamycin: no cytotoxicity; increase in autophagosome (LC3, LC3B-II & beclin-1); enhancement of autophagic effect through Akt/mTOR pathway; decrease of inflammatory factors; decrease of angiogenic cytokine.	Rapamycin but not 3-MA: autophagic activation to prevent cell death through activating Akt/mTOR signaling pathway & decreasing inflammatory factors & angiogenic cytokines.
[58]	Mithramycin A (MTM: an sp1 inhibitor)	To investigate the protective effect of the Sp1 inhibitor, MTM, against retinal damage in vitro.	***In vitro:*** A2E/BL-induced retinal degeneration in ARPE-19; cell viability (MTS); ELISA; ROS (DHE); gene expression (qRT-PCR); protein expression (Western blot); immunocytochemistry; transfection.	MTM: decrease of cell viability (dose-dependent); inhibition of Sp1 (specificity protein 1) & beta-secretase 1 (BACE1); decrease in AB accumulation; recovery of nuclear membrane & mitochondria damage.	MTM: protective effect against retinal damage by inhibiting the overexpression of BACE1.
[83]	Naloxone (an opioid receptor antagonist)	To investigate the protective effects against retinal damage & underlying molecular mechanisms of action of naloxone in vitro & in vivo.	***In vivo:*** Ccl2-/- /Cx3cr1 -/- DKO & WT C57BL/6 mice; fundoscopy; histopathology (H&E); immunohistochemistry; A2E (HPLC); gene expression (qRT-PCR); serum nitrite.	Naloxone: reduction of focal retinal lesions, loss of photoreceptors & ocular A2E; decrease in expression of proinflammatory cytokines, TLR4, TNF-α, ILβ. & serum nitrite but increase in IL-10 expression; decrease in retinal microglia accumulation & activation in the outer retina.	Naloxone: significant reduction of the progress of retinal lesions through modulation of microglia accumulation & activation at the site of retinal degeneration, possibly mediated by inhibition of the proinflammatory cytokines NO, TNF-α, ILβ.
			In vitro: LPS induced- mouse retinal microglia cells from C57BL/6 mice; gene expression (qRT-PCR).	Naloxone: suppression of LPS-induced proinflammatory genes (IL-1β, IL-10, TLR-4, TNF-α).	Naloxone: inhibition of proinflammatory molecules of NO, TNF–α & ILβ.
[41]	N-Acetylcysteine amide (NACA)	To investigate the protective effects & underlying molecular mechanisms of action of NACA against RPE cell death in vitro & in vivo.	***In vitro:*** tBHP-induced retinal damage in ARPE-19 cells; cell viability (FACS); ROS (DCFDA); cell morphology (inverted microscope); oxidative stress markers (GSH & MDA levels & GPx activity); transepithelial electrical resistance (TEER).	NACA: no cytotoxicity; prevention of the decrease in TEER (maintenance of cellular homeostasis); significant reduction of ROS production; prevention of the increase in MDA levels; increases of cellular GSH level & GPx activity.	NACA: protective effects against retinal damage through antioxidant activity, a novel treatment in rescuing retinal function & preventing vision loss secondary to retinal degenerative diseases, including AMD.
			In vivo: BL-induced 129/SvlmJ mice; ERG; ONL; histology (H&E).	NACA: significant preservation of photoreceptor cell density & RPE integrity; significant prevention of the reduction of the peak amplitude of scotopic a- & b-wave & photopic b-wave.	

[23]	OT-674 (the reduction product of the nitroxide tempol)	To evaluate the protective effects of OT-674 on suppressing photooxidative processes in RPE cells.	***In vitro:*** A2E/BL-induced photo-oxidation in ARPE-19 cells; cell viability (MTT); A2E (HPLC).	OT-674: protection against cell death (concentration-dependent); no cytotoxicity; attenuation of photo-oxidation-associated consumption in A2E; conservation (reduction) of A2E levels; protection against A2E oxidation by quenching singlet oxygen.	OT-674: a potent antioxidant that suppresses photooxidative processes generated in cultured RPE cells by the lipofuscin fluorophore A2E.
[43]	Phenyl-N-tert-butylnitrone (PBN, a free radical spin trap)	To evaluate the protective effects & underlying molecular mechanisms of action of PBN against retinal damage in an animal model of AMD.	***In vivo/Ex vivo:*** BL-induced retinal damage in albino SD rats & BALB/c mice; ERG; histopathology (H&E); rhodopsin regeneration; retinal RDH activity (mouse retinal microsomes); isomerohydrolase activity (enzyme assay); PBN (HPLC).	PBN: pretreatment, but not after BL exposure, complete protection against light-induced loss of retinal function (rod a- & b- wave) with a marked reduction in the rate of recovery of rod photoresponses; no effect on cone function; significant inhibition of rhodopsin recovery; no significant inhibition of retinal RDH activity; almost complete inhibition of 11-cis-retinol generation (inhibition of RPE65).	PBN: potent inhibition of rhodopsin regeneration & recovery of rod photoreceptor responsiveness after bleaching through inhibition of RPE65; no inhibition of cone visual cycle, thus not anticipated to affect diurnal vision.
[28]	Phenyl-N-tert-butylnitrone (PBN) & PBN-derivatives (PBNDs)	To develop and investigate the protective effects of PBN & PBNDs on the visual cycle & light-induced retinal degeneration *in vitro & in vivo.*	***In vitro:*** Bovine RPE microsomes; isomerase activity (HPLC). ***In vivo:*** White light-induced retinal damage in SD rats; ERG; rhodopsin (spectroscopy); histopathology (H&E); protein expression (Western blot). BALB/c mice; rhodopsin (spectroscopy). Baboons (*Papio anubis*); rhodopsin (spectroscopy).	PBN & PBNBs: maintenance (90%) of photoreceptor cells; significant reduction of visual cycle rate in mice & balloon eyes; 75-80% recovery of bleachable rhodopsin.	Eye drops of 5% 4-CH3-PBN: most effective in inhibiting the generation of bleachable rhodopsin. PBN-related nitrones: reach RPE by systemic & topical application and slow the rate of rhodopsin regeneration, thus visual cycle in mice & baboon eyes.
[30]	Raloxifene (SERMs: selective estrogen receptor modulators) & other SERMs, e.g., Clomiphene, Toremifene, Tamoxifen, Afimoxifene, Endoxifen, Ospemifene, Bazedoxifene, MB-001 & Emixustat	To investigate the preventive effects of raloxifene & other SERMs to mitigate the effects of atRAL (all-trans-retinol)-induced toxicity in photoreceptor degeneration in *vitro & in vivo.*	***In vitro:*** atRAL-induced photoreceptor degeneration in human bone osteosarcoma epithelial (U2OS) cells; cell viability (luminescence); calcium influx (fluo-3 AM & Hoechst 33342; other cells-NIH3T3, ARPE19, Chinese hamster ovary, HEK293, and MCF-7); gene expression (qRT- PCR & RNA sequencing; other cells-MCF-7).	atRAL: increase in intracellular calcium & cellular apoptosis (dose-dependent); decrease of U2OS. MB-001 & emixustat: reduction of intracellular calcium dose-dependent). Raloxifene, Clomiphene, Toremifene, Tamoxifen, Afimoxifene, Endoxifen, Ospemifene & Bazedoxifene: maintenance of calcium homeostasis (EC_{50} < 30 µM).	SERM Raloxifene: structural & functional neuroprotective effects in the retina. SERM compounds: protection of photoreceptors from light damage through a cell non-autonomous mechanism & unidentified target.
			In vivo: Light-induced retinal degeneration in *Abca4*$^{-/-}$/*Rdh8*$^{-/-}$ mice; retinal morphology & function (SD-OCT, SLO & ERG); gene expression (qRT-PCR & RNA sequencing).	Raloxifene: preservation of both a- & b-wave ERG responses. Raloxifene & Clomiphene: high preservation of retinal morphology; a few autofluorescence spots in the superior fundus region.	

[66]	Ro 25-6981 (NR2B-selective *N*-methyl-*D*-aspartate --NMDA receptor antagonist)	To identify NMDA signaling as a novel mechanism for scavenging of A2E in human RPE cells.	***In vitro:*** A2E/BL-induced retinal damage in ARPE-19 cells (ATG5-deficient); cell viability (WST-8); A2E degradation (A2E-BDP fluorescence); cell morphology (confocal microscopy); gene expression (qRT-PCR); protein expression (Western blot); autophagic flux (laser scanning microscopy).	Ro 25-6981: no cytotoxicity; significant reduction of lysosomal A2E; increase of *LC3-II* & decrease of *p62* levels (time & concentration-dependent); restorage of impaired autophagy flux.	Ro 25-6981: effective clearance of A2E in human RPE cells mediated by autophagy.
[29]	(±)-RPE65-61 (a novel visual cycle inhibitor)	To evaluate the inhibitory activity of (±)-RPE65-61 on 11-cis-retinal regeneration *in vitro & in vivo.*	***In vitro:*** Bovine RPE microsomes; retinol isomerase assays (HPLC); endogenous retinoids (HPLC).	(±)-RPE65-61: inhibition of retinol isomerase activity (IC_{50} =80 nM, uncompetitive)	(±)-RPE65-61 (a novel visual cycle inhibitor): attenuation of retinal apoptosis & preservation of retinal function through downregulation of cyclic AMP-GMP synthase stimulator of interferon genes (cGAS-STING).
			In vivo: Light-induced retinal damage BALB/cJ albino mice; Rpe65-Leu450 polymorphism; histopathology (H&E); apoptosis (TUNEL); histopathology (H&E); OCT; retinal thickness; ERG.	(±)-RPE65-61: inhibition of 11-cis-retinal chromophore regeneration; prevention of declines of retinal thickness induced by light damage; suppression of RPE65 activity preserves photoreceptors; a significant increase in scotopic a-& b-wave amplitudes; suppression of *cGAS* & *STING* expression; upregulation of phosphorylated NFκB-p65 subunit (*p-p65*); significant reduction of TUNEL positive cells & increase of apoptosis.	
[31]	Taurocholic acid (TCA)	To investigate the protective effects of TCA against retinal damage to protect against RPE damage *in vitro.*	***In vitro:*** Paraquat-induced oxidative stress in primary human HRPEpiC & RF/6A macaque choroidal endothelial cells; cell viability (Alamar blue); cell proliferation (BrdU assay); cell migration (scratch-wound migration assay; tube formation (tube formation assay); tight junction (immunofluorescence); paracellular permeability (TEER).	TCA: no cytotoxicity; protection against paraquat-induced tight junction damage (dose-dependent); promotion of RPE cell & reduction of VEGF-induced choroidal endothelial cell migration & tube formation.	TCA: protective effects against both degenerative & neovascular AMD with antiangiogenesis activity.
Essential elements					
[44]	Pyridoxamine (a form of vitamin B6)	To investigate the preventive effects of pyridoxamine against Isolevuglandin (isoLGs)-induced retinal damage in the mouse model.	***In vivo:*** Bright light-induced retinal damage in pigmented B6129SF2/J female mice; B6 vitamers (LC/MS); total Lys-iso[4]LGE_2 (MS); Lys-iso[4]LGE_2 localization (immunostaining & fluorescence microscopy); morphology (TEM).	PM: increase of B6 Vitamers' levels in mouse serum & retina; reduction of IsoLG adduction; reduction, but not complete elimination of the intensity of anti-iso[4]LGE2 fluorescence; reduction of alteration of mitochondrial morphology.	PM: effective scavenger of isoLGs in mouse retina, diminishing post-translational modification of retinal proteins through lipid peroxidation products.

[46]	Vitamin A enriched with the stable isotope deuterium at carbon twenty (C20-D3-vitamin A)	To evaluate the effect of deuterium enrichment of vitamin A at the C20 position to slow the formation of vitamin A dimers *in vitro & in vivo.*	***In vitro:*** A2E &C20-D3 formation (HPLC); A2E competition (MS).	A2E formation: 7 times slower for C20-D3-retinaldehyde than retinaldehyde. C20-D3 -retinaldehyde: formation of ATR-dimer 12 times less rapidly than unlabeled retinaldehyde.	C20-D3-vitamin A: decrease of A2E formation in animals with no obvious defects in retinoid processing, long-term approach to retard vitamin A dimerization & reduction of lipofuscin deposition & the progression of common degenerative eye diseases.
			In vivo/Ex vivo: ICR mice (vitamin A & C20-D3) & CD IGS female rats; A2E (HPLC); liver vitamin A (APCI MS).	C20-D3-vitA: 68% less A2E relative to mice administered normal vitamin A; 45% less A2E. Fenretinide or TDH: 58& & 40% less A2E relative to control. No significant difference in decrease 4in A2E level among all three inhibitors of A2E4 biosynthesis.	
Growth factors					
[79]	PEG-POD-CDNF (polyethylene glycol-peptide for ocular delivery-cell-derived neurotrophic factor)	To investigate the protective effect of PEG-POD-CDNF against light-induced photoreceptor apoptosis *in vivo.*	***In vivo/Ex vivo:*** BL-induced retinal damage in BALB/c mice: ERG; histopathology (DAPI); GFAP staining; gene expression (qRT-PCR); apoptosis (TUNEL, caspase-3/7 activity); ONL/INL ratio.	Significant reduction of apoptosis; increase in ONL thickness; increase of functional response (ERG) 7-day post-light treatment.	PEG-POD nanoparticles: an important step in the development of retinal degeneration.
[40]	Pigment epithelium-derived factor (PEDF)	To evaluate the neuroprotective & anti- inflammatory effects of PEDF on focal retinal lesions in *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO mouse model.	***In vivo:*** *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO & WT C57BL/6 mice; gene expression (qRT–PCR); protein expression (Western blot); retinal imaging (fundoscopy); clinical grading; A2E (HPLC); histopathology (H&E); apoptosis (TUNEL); immunohistochemistry. ***In vitro/Ex vivo:*** Mouse RPE from *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO& WT mice; gene expression (qRT–PCR); protein expression (Western blot); PEDF (ELISA)	PEDF: fewer/smaller photoreceptor damages; significant reduction of A2E; a significant increase in ONL thickness; decrease of apoptosis; no significant changes in *Fasl*, *Fas* & *Bcl2*; a significant decrease in *Bax*; inhibition of angiogenetic & inflammatory molecules through reduction of the expression of TNFα, IL1β, IL17a, iNos & VEGFα transcripts.	PEDF: potent stabilization of focal photoreceptor degeneration in DKO rd8 mice via anti-apoptotic, anti-inflammatory & anti-angiogenic pathways.
[39]	Platelet-derived growth factor (PDGF)-C	To evaluate the neuroprotective & antiapoptotic effects of PDGF-C on focal retinal lesions in *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO on C57BL/6N mice, a model for progressive & focal retinal degeneration.	***In vivo:*** *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO & WT C57BL/6 mice; gene expression (qRT–PCR); protein expression (Western blot); retinal imanging (fundoscopy); retinal vessels (Dil stain); A2E (HPLC); histopathology (H&E, TEM); apoptosis (TUNEL); immunohistochemistry.	PDGF-C: significant improvement with fewer & smaller deep retinal lesions; tendency to reduce the levels of A2E; significant increase in *Fas* & *Bax* transcript levels; decrease in *Fasl* & *Bcl2;* no induction of leakage & neovascularization.	Neuroprotective & survival effects of PDGF-C: stabilization of focal photoreceptor degeneration in DKO *rd8* mice through antiapoptotic pathway without inducing retinal angiogenesis; a novel treatment for retinal degeneration diseases such as AMD.

Recombinant proteins					
[37]	TSG-6 (recombinant protein)	To evaluate the effects of an intravitreal administration of TSG-6 on the retinal lesion of *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO mice.	***In vivo:*** *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO & WT C57BL/6 mice (intravitreal); retinal visualization (fundoscopy); histopathology (H&E, TEM); A2E (HPLC); gene expression (TaqMan array & qRT–PCR).	TSG-6: decrease of lesion size & number in right eyes; no difference in the amount of A2E; downregulation of IL-17α & TNFα expression.	Intravitreal administration of recombinant TSG-6: stabilization of retinal lesions in *Ccl2*$^{-/-}$ */Cx3cr1* $^{-/-}$ DKO ^{rd8} mice, possibly through modulation of ocular immunological gene expressions, especially IL-17α.
[72]	Recombinant manganese peroxidase (rMnP)	To present a proof-of-concept study for an enzyme-based therapy to remove these retinoids, modeled on traditional enzyme replacement therapy in *vitro & in vivo.*	***In vitro:*** Recombinant manganese peroxidase (rMnP) *P. pastoris* (yeast); protein purification; glycoanalysis (gel shift). ARPE19, RAW264.7 cells & Primary human RPE cells; cell viability (resazurin); apoptosis (flow cytometry); A2E degradation (HPLC, spectrophotometry); DMP activity (spectrophotometry); mannan uptake (FITC stain, spectrophotometer).	rMnP: A2E break down (EC_{50}= 20μM); efficient removal of A2E; prevention of A2E-mediated cytotoxicity; mannose receptor (CD206)-dependent uptake into RAW264.7 cells; no expression of mannose receptors (CD206) in APRE-19; passage-dependent downregulation of mannose receptors in primary RPE cells.	Clear proof-of-concept for using heterologous enzymes to degrade RPE lipofuscin following an enzyme replacement therapy approach.
			In vivo: C57/BL6 mice (intravitreal); ERG; histopathology (H&E); A2E (HPLC); cytokines (ELISA).	Significant reduction of A2E; increase in serum anti-rMnP antibodies (repeated doses). Intraocular half-life = 9.6 hours.	
Stem cells					
[69]	Human adipose mesenchymal stem cells (hAD-MSC)	To explore the molecular mechanisms involved in the rescue effect of hAD-MSC against retinal damage in RPE cells.	***In vitro:*** $NaIO_3$-induced retinal damage in ARPE-19 cells; cell viability (WST-8); apoptosis (flow cytometry; TUNEL); mitochondrial morphology (fluorescence); gene expression (qRT-PCR); protein expression (Western blot); cytokines (ELISA).	hAD-MSC: rescue effect on retinal damage; mitigation of oxidative stress-mediated mitochondrial pathway; suppression of the expression of NLRP3, caspase-1 & its downstream IL-1β; significant elevation of the percentage of $NaIO_3$-treated cells in S-phase of the cell cycle.q	hAD-MSC: suppression of NF-κB pathway & maintenance of mitochondrial function downstream of lysosomal de-stabilization, which in turn improved RPE viability.
Intraocular lens					
[47]	BL-filtering intraocular lenses (IOL)	To determine the effects of BL on the behavior of RPE cells & their potential mitigation by BL-filtering intraocular lenses (IOL)	***In vitro:*** A2E/BL-induced retinal degeneration in ARPE-19 & primary RPE cells; ROS (DCFDA); IOL (single-piece acrylic clear UV filtering & Natural yellow UV & BL-filtering); cell viability (WST-8).	Cytotoxic effects of BL on ARPE-19 cells & primary RPE cells: increase in ROS production. Yellow-pigmented IOL: reduction of cytotoxicity.	BL-filtering devices: a promising strategy to reduce retinal damage and delay the onset of AMD.

Table 3 Herb-derived compounds and non-herb-derived molecules.

Ref	Compound/Extract	Objectives	Study models & Methodology	Main findings	Conclusions
[36]	Lutein (carorenoid) & Zeaxanthin (anthocyanin), Docosahexaenoic acid (DHA) & Eicosapentaenoic acid (EPA) (unsaturated fatty acids)	To evaluate the preventive effects of a diet supplemented with lutein, zeaxanthin, DHA & EPA in the retinas of Ccl2-/-/Cx3cr1-/--deficient mice on Crb1rd8 background.	***In vivo:*** Ccl2-/- /Cx3cr1 -/- DKO mice and C57BL/6 rd8/rd8 (WT) mice; gene expression (qRT–PCR); PGE2 (ELISA); retinal lesion (fundoscopy); A2E (LC/MS); histopathology & ONL (H&E); retinal ultrastructure (TEM); fatty acids (GC).	Supplementation of DHA & lutein: significant decrease of the expressions of NOS, TNF-α, COX-2, IL-1β & Vegf; no change in serum PGE2; significant reduction of A2E levels & retinal lesions & preservation of ONL. Higher retinal concentrations of EPA & DHA in A-DKO mice.	Supplementation of DHA & lutein: improvement of RPE & photoreceptor metabolism, possibly through anti-inflammatory effects.
[27]	Norbixin & PPAR–α, –β/δ, –γ & RXR antagonists	To evaluate the protective effects of norbixin & PPAR–α, –β/δ, –γ & PΞP antagonists against retinal damage *in vitro*.	***In vitro:*** Binding of RXR-α & PPAR-α & γ A2E-induced inflammation & angiogenesis in RPE cells (pig eyes); PPAR, RXR, AP-1 & NF-κB (luciferase activity); gene expression (qRT-PCR); protein expression (Western blot).	Norbixin: binding to all three isoforms of PPAR, but inhibiting only PPAR & RXR transactivation; reduction of protein kinase B (AKT) phosphorylation, NF-κB & AP-1 transactivation & mRNA expression of IL-6, IL-8 & VEGF; increase of MMP-9 & CCL2 mRNA expression. Selective PPAR–α, –β/δ & -g antagonists: inhibition of IL-6 & IL-8 expression; PPAR–γ antagonist: inhibition of NF–κB. A cocktail of three PPAR antagonists & HX531 (antagonist of RXR): reproduction of norbixin effects on inflammation. HX531: reduction of inflammation & angiogenesis.	Norbixin: modulation of the expression of molecules involved in angiogenesis & inflammation stimulated by A2E critical for AMD evolution. A2E: induction of the transactivation of RXR & PPAR.

4. DISCUSSION

4.1. AMD pathogenesis and potential drug targets

RPE cells are equipped with antioxidants that maintain the pro-oxidant/antioxidant balance. Endoplasmic reticulum (ER) stress is the mechanism underlying the dysfunction and apoptosis of RPE cells and is a primary pathogenesis of AMD[94]. The retina is particularly susceptible to oxidative stress due to its high levels of photo-sensitizers and pigments, its high consumption of oxygen, intense exposure to visible light[95], and extreme oxygen tension in the macular region[96-97]. The ageing process reduces antioxidant capacity, leading to oxidative stress (excess OH, -O_2, H_2O_2, $NO^{\bullet}$ and $ONOO^{-}$). The consequences of oxidative stress include, among oxidized species, the formation of lipid peroxidation products that can damage biomolecules like proteins, phospholipids, and DNA, eventually contributing to alterations in cell and tissue homeostasis and AMD. ROS can also be produced by A2E photo-oxidation generating singlet oxygen[98]. As A2E displays numerous conjugated double bonds in the structure, it is prone to oxidation and releases toxic metabolites such as endoperoxides and epoxides[98]. The lipid peroxidation process is also responsible for A2E cleavage, liberating cytotoxic carbonyl species. When formed in toxic concentrations, these reactive aldehydes affect the lipid membrane's fluidity and damage DNA and cellular proteins[99-100]. The nuclear factor erythroid 2-related factor 2 (Nrf2) is one of the most essential transcription factors that modulate the antioxidant system. It controls and coordinates expression of the antioxidant response element (ARE)-regulated genes of the downstream detoxifying enzymes, such as NAD(P)H quinone oxidoreductase-1 (NQO-1) and haem oxygenase-1 (HO-1) by binding to the promoter[101-103]. Nrf2 is modulated by PI3K/Akt signaling pathway, which also plays a crucial role in cell proliferation and apoptosis. Akt-Nrf2 activation is thought to be an efficient factor involved in AMD[104].

BL irradiation on A2E-accumulated RPE cells causes DNA damage and apoptosis. Apoptosis occurs through two broad pathways, *i.e.*, the intrinsic or mitochondrial pathways and the extrinsic pathway or death receptor pathway[105]. Caspases are the key players in the apoptotic pathway, especially the effector caspases, caspase-3 and caspase-9[106]. One of the critical elements in the mitochondrial apoptosis pathway is the Bcl-2 (B-cell leukemia/lymphoma 2) family[107-108]. The Bcl-2 family controls mitochondrial outer membrane permeability and can enhance or inhibit apoptosis. The levels of antiapoptotic proteins such as Bcl-2 and the expression of proapoptotic factors such as Bax are associated with the survival of cells under stress[109-112]. The extrinsic pathway is initiated by the binding of transmembrane death receptors (Fas, TNF receptor, and TRAIL receptor) to their respective ligands (FasL, TNF, and TRAIL), with the aid of the adaptor molecule FADD to activate membrane-proximal caspases[113]. When A2E-accumulated RPE cells are illuminated with BL, the upstream transcription factors of caspase-3, such as c-Abl, p38, p53 and JNK, act as a part of the cell's response to this type of photooxidative stimuli, which in turn exerts an antiapoptotic effect by upregulating c-Jun *N*-terminal kinases (JNK)[114]. c-Abl is considered the key regulator of p53 and upregulates the transcriptional activity of p53[114].

4.1.1. Role of inflammation in retinal damage and cell death

Inflammation also plays an essential role in retinal injury and cell death. Toll-like receptor 4 (TLR4)-mediated signaling pathways have been revealed to activate nuclear transcription factor-κB (NF-κB). TLR-4 is critical to the regulation of multiple proinflammatory genes, including cytokines, chemokines, cyclooxygenase-2 (COX-2), interleukin (IL)-6, IL-8, and inducible nitric oxide synthase (iNOS) [115]. Therefore, the activation of NF-κB is proposed as a cause of ocular inflammatory disease.

4.1.2 Inflammasomes and their role in AMD pathogenesis

Inflammasomes are components of the innate immune response that have recently emerged as crucial controllers of tissue homeostasis. In particular, the nucleotide-binding domain, NOD-like receptor family pyrin domain-containing 3 (NLRP3), is a complex platform involved in the autoactivation of caspase-1 and, subsequently cleavage of proinflammatory cytokines, including interleukin (IL)-1β and IL-18, resulting in pyroptosis, a form of programmed cell death perturbations of extracellular or intracellular homeostasis related to innate immunity[116-117]. This process is a caspase-1-dependent type of cell death that is mediated by the cleavage of gasdermin D and the subsequent formation of structurally stable pores in the cell membrane. Through these pores formed by gasdermin proteins, cytosolic contents are released into the extracellular space and act as damage-associated molecular patterns, which are pro-inflammatory signals.

NLRP3, widely studied inflammasome, was shown to be involved in various immune and inflammatory diseases, including AMD[118]. Previous studies have indicated that activated NLRP3 aggravates RPE death and potential visual loss. Meanwhile, NLRP3 activation in the immune cells accumulating in the retinal area also contributes to the pathogenesis of AMD[118-119]. Conversely, blocking the -NLRP3-mediated

inflammasome signaling in the RPE slows down the AMD progress[120]. In general, pyroptosis is a defence mechanism protecting cells from infection by inducing pathological inflammation[121]. However, persistent inflammation leads to AMD[122]. It was reported that pyroptosis could increase RPE cells' susceptibility to photooxidative damage-mediated cell death and contribute to RPE degeneration[122]. Moreover, activation of pyroptosis mediated *via* NLRP3/caspase-1 signaling is the primary mechanism of cellular death in AMD[117,119,123]. This suggests that inhibiting pyroptosis, particularly drugs that target NLRP3, is an essential insight into AMD intervention.

Oxidative stress is a major contributor to retinal diseases by directly damaging retinal cells and by triggering inflammation through the activation of pathways such as NF-κB, inflammasomes, and microglial activation. The cycle of oxidative damage and inflammation accelerates the progression of diseases like AMD and diabetic retinopathy, leading to vision impairment or loss. Understanding these mechanisms highlights the importance of antioxidant therapies and anti-inflammatory strategies in treating and preventing retinal diseases[29,88].

4.2. Current therapeutic approaches for AMD

Based on the mechanisms of pathogenesis of AMD, current therapeutic approaches to search for effective candidates to prevent the disease progress mainly focus on (i) reducing the levels of reactive oxygen intermediates or reducing the downstream oxidative products (lipid oxidation products), (ii) reducing inflammation-associated processes, (iii) reducing cell death *via* apoptosis, autophagy, or pyroptosis, and (iv) reducing the accumulation of A2E in the RPE by slowing down the visual cycle through inhibiting RPE65, the key enzyme in the visual cycle. Another strategy being studied is the inhibition of the angiogenesis process. The proposed molecular targets of action of potential herbs/herb-derived compounds, including synthetic compounds, are summarized in **Figure 3**.

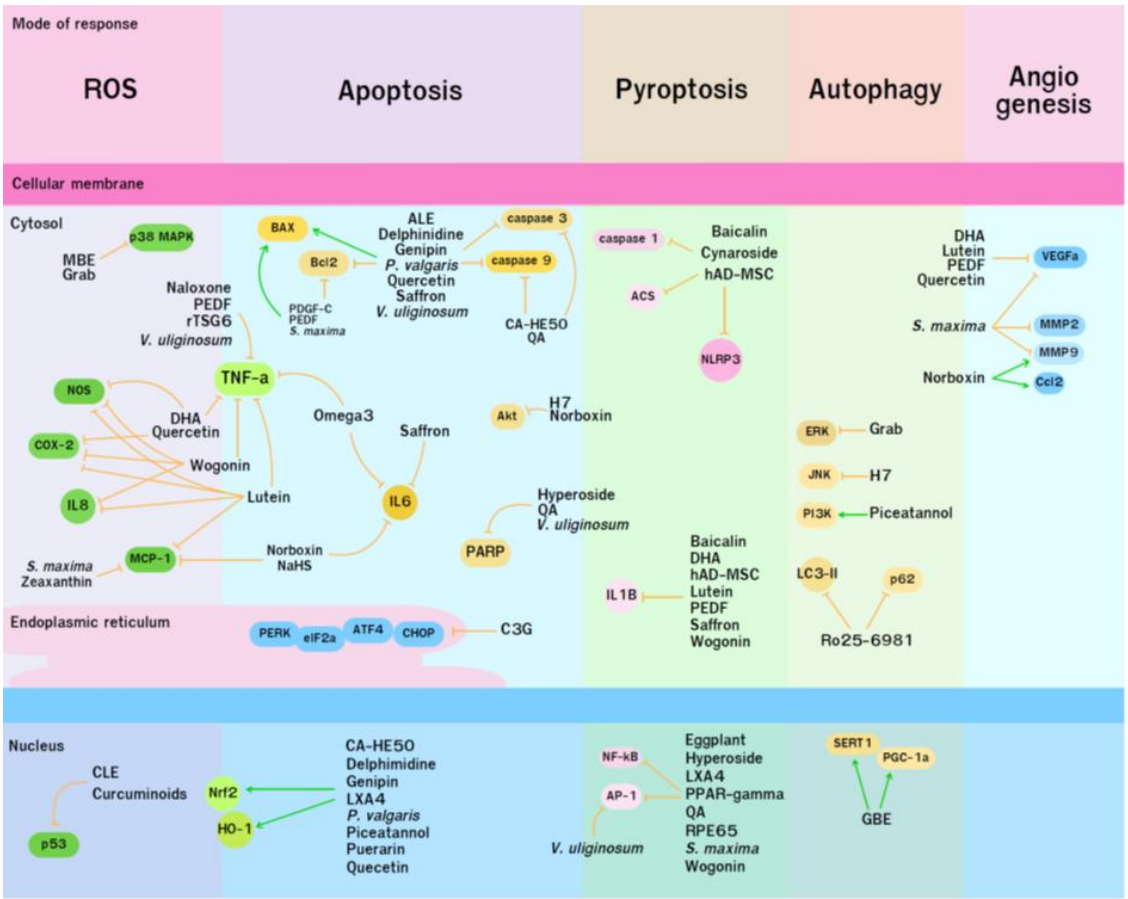

Figure 3. The proposed molecular targets of action in AMD (in cellular component and nucleus of the retina cekks) of potential herbs/herb-derived compounds, including synthetic compounds.

4.3. Potential herbs and herb-derived compounds for AMD

Several herbs and herbal products have shown promise in alleviating BL/A2E-induced retinal damage *in vitro* and *in vivo* models. Many studies suggest naturally occurring antioxidant agents can ameliorate age-related changes associated with oxidative damage in RPE cells. Flavonoids, anthocyanins, carotenoids, polyphenols and diarylheptanoids have extensively been investigated for their antioxidant properties in ARPE-19 and primary human RPE cells[21,58]. Flavonoids are structurally heterogeneous, polyphenolic compounds present at high concentrations in fruits, vegetables and other plant-derived foods, such as tea and other beverages. They are regularly consumed in the human diet[124]. Flavonoids have also shown anti-inflammatory activity[125]. Anthocyanins are a group of colored (deep red, purple, and blue) pigments found in fruits and vegetables, *e.g.,* mulberries, blue berries, raspberries, red grapes, and pomegranates. They exert multiple protective effects on retinal cells, including activating antioxidant pathways, reducing inflammation, inhibiting cell apoptosis, and ameliorating damage caused by lipid peroxidation products[126]. Carotenoids are yellow, orange, and red pigments synthesized by plants. The most common carotenoids in diets are α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene. Observational studies have suggested that diets rich in lutein and zeaxanthin may help slow the development of AMD. Randomized controlled trials in subjects with AMD have found that lutein and zeaxanthin supplementation improves visual acuity and slows the progression to advanced AMD in subjects with AMD[75,149]. Polyphenols are naturally occurring compounds found mainly in fruits (*e.g.* resveratrol), vegetables, cereals and beverages. They appear to play an essential role as angiogenesis inhibitors, but their effect on AMD is still unclear[70-71,89].

The most common underlying mechanisms for prevention of retinal damage involve antioxidant activities such as *Arctium lappa*[61], astaxanthin[33], betulinic acid[51], catechin[71], *Centella asiatica*[24], curcumin[192-196], chlorogenic acid [89], cymaroside [56], cyanidin-3-glucoside[76], delphinidin[73], genipin[93], glabiridin[34], lutein[49,67,75], maqui berry and constituents[25], *Panax ginseng*[54], phloroglucinol[71], piceatannol[68], *Prunella vulgaris* [61], puerarin[88], quercetin and derivatives[35,64,69-70,89], resveratrol [17,48,70], *Ribes nigrum* or black current[84], *Sabanum melongena*[77], *Solanum lycopersicum* or tomato[52], and zexanthin[49]. Several exert direct/indirect antiapoptotic activities such as *Artium lappa*[61], astaxanthin[33], *Centella asiatica*[24], cholorgenic acid[89], *Curcuma longa* and constituents[74], cymaroside[56], cyanidin-3-glucoside[76], delphinidin[73], kaemferol[26], genipin[93], glabiridin[34], lutein[67], maqui berry and constituents[25], myricetin[26], *Prunella vulgaris*[62], quercetin and derivatives[26,35,40,60,64,89], retroversal[48], and *Spirulina maxima*[53]. Anti-inflammatory activities have been reported with baicalin [85], cymaroside[56], genipin[93], lutein[36,49,67], norbixin[27], *Panax ginseng*[54], *Prunella vulgaris*[62], quercetin and derivatives[35,60,64], *Vaccinium uliglinosum*[59], wogonin[50], and zeaxanthin[36,49]. Antiangiogenetic activities were reported with lutein[36], norixin[42], quercetin[89], *Spirulina maxima*[53], and zeaxanthin[36].

The current systematic review suggests that dietary polyphenols and carotenoids constitute potential novel strategies to prevent the onset and development of AMD. Lutein, zeaxanthin, quercetin and derivatives, and resveratrol are the most investigated compounds, and *Vaccinium uliginosum* is the most studied plant extract. Lutein is a type of carotenoid used in healthcare[127]. The compound forms human macular pigments with zeaxanthin in the retina, inhibiting noxious BL and strengthening the antioxidant defence of RPE cells[49,128]. The sources of lutein are primarily found in dietary origin, for example, green leafy vegetables (*e.g.*, spinach and cabbage), fruits (*e.g.*, grapes and kiwis), egg yolks, and corn[129]. It is reported that the risks of the onset and progression of AMD are negatively correlated with lutein concentration in the macula[130-131].

Lutein and quercetin are the only two compounds that have been reported for their broad activities in the prevention of retinal damage, *i.e.*, antioxidant[35,49,60,67,70,71,75,89], anti-inflammatory[35,36,49,67], anti-apoptosis[26,35,67,89], and anti-angiogenesis[36,89] activities. Lutein and zeaxanthin supplementation contributes to the prevention of AMD by increasing the macular pigment density and protecting RPE cells against oxidative stress[49,132]. Both compounds exhibited moderate inflammatory activities in cultured RPE in response to photooxidation (protecting the proteasome from oxidative damage). The diet supplemented with lutein, zeaxanthin, and polyunsaturated fatty acids such as docosahexenoic acid (DHA) and eicosapentanoic acid (EPA) was shown to significantly decrease the expressions of NOS, TNF-α, COX-2, IL-1β, and VEGF in the knockout mouse model[36]. RPE and photoreceptor metabolism improved with the supplementation of lutein and DHA based on lower A2E levels, fewer retinal lesions, and preservation of the outer nuclear layer (ONL). Lutein exhibits potential effective antioxidant (reduction of ROS) and anti-inflammatory activities (increase in transcription levels of IL-6, IL-8, and TNF-α). It reduced the proportions of RPE cells in the G_2/M phase, activated cyclin-dependent kinase 1 (CDK1) and CDC25C, and decreased cyclin B1[67]. In a randomized controlled trial (RCT) in 56 middle-aged Taiwanese subjects with early-stage AMD, daily supplementation with lutein showed remarked antioxidant enzyme activity and plasma total

antioxidant capacity (significant reduction of total free radicals and thio barbituric acid reactive substance (TBARS) levels, an increase of glutathione content and anti-oxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (Gpx) levels). In another RCT study in 60 early and moderate AMD patients, dietary supplementation with the carotenoid zeaxanthin raised macula pigment optical density (MPOD). It provided unique visual benefits for patients with early atrophic macular degeneration[80]. Lutein and zeaxanthin, as demonstrated in the AREDS trials, are essential components in the fight against AMD, particularly in reducing the progression of the disease in individuals with intermediate to advanced stages. The AREDS 2 findings have led to a widespread shift in AMD treatment guidelines, favoring lutein and zeaxanthin over beta-carotene due to their safety and effectiveness. As ongoing research continues, including the promising AREDS 3, lutein and zeaxanthin are likely to remain central to both the clinical management of AMD and preventive strategies aimed at preserving vision in aging populations[197-199].

Saffron (*Crocus sativus* L.) is a brightly-colored spice high in health-promoting compounds, such as carotenoid antioxidants. Research findings suggest numerous therapeutic properties of saffron, such as anti-inflammatory and antioxidant effects, and it may improve heart health, reduce symptoms of depression and anxiety, improve sleep, and protect eye health. All clinical studies[185-191] demonstrated the potential role of saffron oral supplementation in improving visual function in AMD.

Curcumin (*Curcuma longa*) is a natural product with several pharmacological activities, particularly anti-inflammatory and antioxidant properties. However, research concerning its potential role in AMD has been limited. *In vitro* studies showed significant protection of curcumin and curcuminoids against photo-oxidative damage and apoptosis in RPE cells[74,192-196].

The protective effects of *V. uliginosum* extract and its fractions containing polyphenol components against retinal damage in RPE cells, including their underlying mechanisms of action, were investigated *in vitro* and *in vivo* [65,91]. The extract and the fractions significantly reduced BL-induced ARPE-19 cell death, downregulating the expression of cleaved caspase-3 and Bax/Bcl-2. They inhibited intracellular A2E accumulation and A2E oxidation–mediated effects on cell death. In the *in vivo* model, the fractions and some of the isolated compounds (quercetin, hyperoside or quercetin-3-O-β-D-galactopyranoside, quercetin-3-O-α-L-arabinopyranoside, cyanidin-3-O-β-D-glucopyranoside, myricetin, myricetin-3-O-β-D-galactopyranoside, syringetin-3- O-β-D-galactopyranoside, methylchlorogenate, chlorogenic acid, loganic acid, and 6,7 dihydromonotropein methyl ester or splendoside) prevented the degeneration of ONL nuclei and decreased photic damage. Quercetin, the polyphenol flavonoid of the flavonol family, is the most effective active compound from *V. uliginosum*. It is the most investigated member of the flavonoid family and is also thought to be one of the most prominent dietary antioxidants. The compound inhibited retinal cell death and significantly increased the number of photoreceptors and bipolar cells in BL/A2E-induced photoreceptor death in primary retinal cell cultures[26]. The anti-inflammatory effect of quercetin was investigated in cultured RPE monolayer cells and in the retinas of the *Ccl2/Cx3cr1* double knock-out (DKO) mice, which spontaneously develop progressive retinal lesions mimicking AMD, with oxidative stress and inflammation-related retinal degeneration[35]. Quercetin protected the cells from apoptosis under oxidative stress induced by H_2O_2 *via* inhibiting pro-inflammatory molecules and direct inhibition of the intrinsic apoptosis pathway. Bax, FADD, caspase-3, and caspase-9 expressions were significantly downregulated, and the transcriptions of Bcl-2, Bcl2/Bax ratio were significantly enhanced. The transcriptions inhibiting the pro-inflammatory cytokines TNF-α, COX-2, NO, and INOS were downregulated. The underlying mechanisms are likely due to insufficient suppression of ocular inflammatory and apoptotic pathways in the eyes. In the H_2O_2-induced oxidative stress in *Ccl2/Cx3cr1* knock-out DKO mice, however, quercetin (25 mg/kg/day) did not improve the retinal lesions. In the pigmented rabbit model[89], quercetin produced protective effects on retinal degeneration and prevented the reduction of ONL thickness. The underlying mechanisms were through the inhibition of oxidative stress (upregulation of HO-1), inflammation, apoptosis (downregulation of Bax and activation of Bcl-2 expression), and angiogenesis (reduction of VEGF and HIF-1α expression). Furthermore, quercetin was shown to protect against the loss of retinal layers and removed intracellular A2E from AREP-19 cells by the suppression of poly ADP-ribose polymerase (PARP) cleavage, NF-κB and activator protein 1 (AP1) activities, together with activation of complement 3 (C3) and the expression of cytochrome P450 1A1 (CYP1A1) and cytochrome P450 1B1 (CYP1B1)[64]. Quercetin-3-O-β-D-galactopyranoside (hyperoside), the derivative of quercetin, was also found to be a potential application to prevent the onset and development of AMD. The compound effectively suppressed A2E accumulation and PMA-induced NF-κB and AP-1 activity, and PARP cleavage, recovered C3 level, and upregulated AHR target genes expression of CYP1A1 and CYP1B1[70]. It also protected the retinal cells against the decrease in retinal thickness and loss of the number of nuclei in BL-induced BALB-c mice[60,64]. Quercetin conjugated to linoleic or α-linolenic acid (Quer-3-LA and Quer-7-ALA) exhibited promising lipophilic antioxidants, protecting ARPE-19 cells from

A2E-induced cell death more effectively than the parent polyphenol, quercetin[71]. Q-3DHA-7OiP (quercetin lipophenol) was the most potent derivative to suppress photooxidative toxicity initiated in RPE cells by A2E. Overall, the research suggests that quercetin and its derivatives from *V. uliginosum* have substantial potential for preventing the onset and development of AMD through their multifaceted protective mechanisms in the retinal cells.

Resveratrol, a polyphenol in the stilbene family (3,4′,5-trihydroxystilbene), is mainly found in grapes, apples, blueberries, plums, and peanuts. The compound exhibited antioxidant and anti-neovascularization activities in retinal cells[22,133-134]. It strongly inhibited A2E-induced photooxidation and A2E accumulation[22]. Resveratrol and its analog – quer-7-ALA were reported to protect ARPE-19 cells against BL/A2E-induced cell death through the regulation of A2E accumulation, reduction of A2E-epoxidation, and subsequently, prevention of DNA damage and cell death[17,70].

Apart from lutein, zeaxanthin, quercetin and derivatives, and resveratrol, herbs and herb-derived compounds with potential activities in AMD are *Aristotelia chilensis*[25], *Centella asiatica*[24], *Scutellaria baicalensis* and its main compound baicalin[85], genipin[93], norbixin[27,42], *Panax ginseng*[54], and wogonin[50] (**Table 1**). *A. chilensis* (maqui berry) has an exceptionally high concentration of anthocyanins such as delphinidin, cyanidin, delphinidin 3,5-*O*-diglucoside (D3G5G), and delphinidin 3-*O*-sambubioside-5-*O*-glucoside (D3S5G)[135]. The plant extract and its anthocyanins content possess antioxidant[136-137] and anti-inflammatory[138] activities and suppress light-induced photoreceptor cell death by inhibiting ROS production[25]. *C. asiatica* (Gotu Kola or pennywort) has been used in traditional medicine in India, China, Korea, and Southeast Asia to treat various diseases, including wound healing[139]. *S. baicalensis* has been the most widely used traditional Chinese medicine for treating pulmonary diseases, jaundice, and hypertension[140]. Its active constituent, baicalin, was shown to possess various biological properties, including anti-inflammatory and antioxidant activities and targeting NLRP3 inflammasome and NF-κB signaling [141-145]. Genipin, a glycosidic ligand derived from iridoid glycosides, is widely distributed in plants, including Mast and *Eucommia ulmoides*[146]. It showed anti-inflammatory and antioxidant activities in RPE cells[147-150]. It is a specific inhibitor of uncoupling protein 2 (UCP2) involved in modulating the opening of the ion channels on the mitochondrial membrane, inhibiting the production of ROS, thereby suppressing the apoptosis of cells and damage to mitochondria[151-152]. Norbixin (9'-*cis*-norbixin), a PPAR-γ-receptor agonist, is a 6,6'-di-apocarotenoid extracted from annatto (*Bixa orellana*) seeds[153]. *Panax ginseng* berry (fruit) is traditionally used as a medicinal plant in Asia[154] and possesses anti-inflammatory and antioxidant activities[155-158]. It contains significant amounts of ginsenosides phenolic compounds such as chlorogenic acid[156]. Wogonin (5,7-dihydroxy-8-methoxyflavone) is a flavonoid isolated from the root of *Scutellaria baicalensis*, and has been used in traditional Chinese medicine to treat allergies, inflammatory diseases, and cancer[115,159]. It has multiple pharmacological effects, including anti-inflammatory effects.

4.4. Other potential molecules

Non-herbal molecules from different sources/synthetic approaches have been investigated for their preventive effects against retinal damage in AMD (**Table 2**). These include novel visual cycle inhibitors: CU239[32], emixustat hydrochloride[81], (±)-RPE65-62[29], and phenyl-N-tert-buylnitrone (PBNDs)[43], all-trans-retinylamine, farnesylamine[57]; autophagic inhibitors: 3-methyladinine; autophagic activator (rapamycin)[92]; specificity protein 1 (sp1) inhibitor (mithramycin)[58]; recombinant proteins: polyethylene glycol-peptide for ocular delivery-cell-derived nerotrophic factor[79], pigment epithelium-derived factor (PEDF), platelet-derived growth factor (PDGF)-C[39], recombinant TSD-6[37], recombinant manganese peroxidase[72]; chemical compounds: hydrogen sulfide[78], 2-(2-hydroxyethyl cabamate)[86], naloxone[83], N-cetylcyteineamide [41], OT-674 (the reduction product of nitroxide tempol)[23], pyridoxamine[44], Ro25-6981 (NMDA receptor antagonist)[66], selective estrogen modulators[30], taurocholic acid[31], vitamin A-enriched with deuterium[46]; endogenous antioxidant: lipoxin A4[90]; and human tissues: human adipose mesenchymal stem cells (MSCs)[69]. Among these, compounds that inhibit the visual cycle through inhibiting isomerohydrolase RPE65, the key enzyme in the cycle, is the research focus in searching for promising compounds that prevent retinal damage. Most exert a variety of mechanisms to protect retinal cells against damage. Emixustat hydrochloride, the inhibitor of RPE65, appears to be the only compound that did not show promising activity in phase 2b/3 multicenter, randomized, double-masked, placebo-controlled clinical trial in 503 AMD patients[81]. CU239 is a selective non-retinoid inhibitor of RPE65, which suppresses the visual cycle and prevents retinal degeneration. It markedly reduced 11-cis-ROL and acted as a competitive inhibitor of RPE65[32]. (±)-RPE65-61, a novel, non-retinoid compound that acts as an inhibitor of RPE65, was shown to attenuate retinal apoptosis and preservation of retinal function through downregulation of cyclic AMP-GMP synthase stimulator of interferon gene (CGAS-STING)[29]. Phenyl-*N*-tert-butylnitrone (PBN), a free radical spin trap, was shown to protect retinas against light-induced neurodegeneration, probably by slowing down the rate of rhodopsin regeneration by inhibiting RPE65 activity[160].

It potently inhibited rhodopsin regeneration, leading to the recovery of rod photoreceptor responsiveness after bleaching through inhibition of RPE65[43]. Lipoxin A4 (LXA4), an endogenous antioxidant lipid, is one of the most critical lipoxins that plays an effective anti-inflammatory and antioxidant role in several organs by binding to formyl-peptide receptor-like 1 (FPRL1, also referred to as FPR2 or ALXR). LXA4 was shown to prevent oxidative damage of RPE cells by inhibiting oxidative stress and activating the antioxidant system (Nrf2/ARE signaling pathway)[90]. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA, the precursor to DHA) are two major n-3 fatty acids and are concentrated in the retina and retinal vascular endothelium[161-162]. Diet enriched in EPA and DHA ameliorated the progress of retinal lesions, possibly *via* the shunted arachidonic acid pathway, leading to an increase of an-inflammatory derivatives such as PGD_2 and a decrease of proinflammatory derivatives such as PGE_2, LTB4, TNF-α, and IL-6[38]. DHA prevents the apoptosis of photoreceptor cells that otherwise inevitably occurs during their early development *in vitro*[163]. DHA supplementation preserved retinal function at mild-degenerative stages in E4 mice, with the potential for broad preventative therapeutic applications for age-related ocular diseases[55]. DHA-enriched eggs (daily for 6 wk) improved rod photoreceptor and cone-driven inner retinal cell responses in healthy Caucasian older adults, which is required for optimal maintenance and functioning of the retina[87]. Pyridoxamine, a scavenger that reduces the downstream oxidative products, was an effective scavenger of isoLGs in the mouse retina, diminishing posttranslational modification of retinal proteins through lipid peroxidation products[44]. The effects of hydrogen sulfide (H_2S) on inflammation are controversial. The anti-inflammatory effect was shown only when supplied externally by H_2S-releasing compounds, *e.g.*, sodium hydrosulfide, H_2S-NSAID hybrids (HS-sulindac, HS-ibuprofen, HS-naproxen, S-sulindac, S-ibuprofen, and S-naproxen)[164-167]. The exogenous supply of H_2S, either by NaHS or compound 1c produced anti-inflammatory effects in Hcy-induced inflammation in RPE cells[78]. Raloxifene, a selective estrogen receptor modulator (SERM), was shown to produce neuroprotective effects in the retina[30]. PEDF (pigment epithelium-derived factor) is a potent neurotrophic and anti-inflammatory glycoprotein that protects the retinal neurons and photoreceptors against cell death caused by pathological insults[168]. The inhibitory effects of PEDF on focal retinal lesions were investigated in DKO rd8 (*Ccl2(-/-)/Cx3cr1(-/-)* on C57BL/6N [*Crb1(rd8)]*) mice, a model for progressive, focal rd (retinal degeneration). It protected photoreceptors against apoptosis in the rd (retinal degeneration) and rds (retinal degeneration slow), light damage animal models, inner retina against ischemia, and retinal ganglion cells[169-172]. PEDF showed pro-survival and anti-apoptotic activity on R28 cells, a rat retinal progenitor cells in culture[173-174]. It also showed potent stabilization of focal photoreceptor degeneration in DKO rd8 mice *via* anti-apoptotic, anti-inflammatory and anti-angiogenic pathways[40]. PDGF-C is a PDGF family member critical for neuronal survival in the central nervous system. It showed anti-apoptotic effects on focal retinal lesions in *Ccl2(-/-)/Cx3cr1(-/-)* on C57BL/6N [*Crb1(rd8)]* (DKO rd8) background mice, a model for progressive and focal retinal degeneration[175-176]. PDGF-C stabilized focal photoreceptor degeneration in DKO *rd8* mice through an antiapoptotic pathway without inducing retinal angiogenesis[39]. Peptide for ocular delivery (POD) is a novel cationic cell-penetrating peptide (CPP) which, when conjugated with polyethylene glycol (PEG-POD), can deliver plasmid DNA to the retinal pigment epithelium (RPE) of the adult murine retina. PEG-POD nanoparticles containing an expression cassette for glial cell line-derived neurotrophic factor (PEG–POD~GDNF) significantly suppressed apoptosis, increased ONL thickness, and improved functional response (ERG) in BL-induced retinal damage in albino SD rats and BALB/c mice[79]. The bile acids – taurochloric acid (TCA), tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA) were shown to protect against photoreceptor loss in multiple models of inherited retinal degeneration[177-181]. These bile acids have been used in traditional Chinese medicine to treat several physical conditions, including poor vision[177]. In the paraquat-induced oxidative stress in ARPE-19 cells, TCA provided a protective effect against both degenerative and neovascular AMD by reducing VEGF-induced choroidal endometrial cell migration and tube formation[31]. TUDCA and UDCA were reported to target apoptosis in various cell types through multiple actions, including reducing endoplasmic reticulum stress[182] and reducing ROS[183-184].

5. **CONCLUSION**

The potential roles of herbs and herb-derived compounds in preventing AMD have been a research focus, as evidenced by many published articles in recent years. Dietary polyphenols and carotenoids, particularly those containing lutein, zeaxanthin, quercetin, resveratrol, curcumin, and saffron, constitute potential herb-derived compounds to prevent and delay the onset of AMD development. The protective effects are due to their antioxidant, anti-inflammatory, and/or antiapoptotic activities involving various molecular targets and signaling pathways. Other potential compounds inhibit RPE65 (a key enzyme in the visual cycle), particularly CU239. Most of these candidate compounds have been or are currently being investigated *in vitro* and *in vivo* models. However, clinical studies are needed to confirm

the potential uses of these candidate compounds in preventing or treating AMD in humans. Further investigation should be focused on the activities of compounds that target pyroptosis-mediated inflammation and cell death and the angiogenesis processes in the retina.

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Author contribution

Investigation, K.K.; Data curation, K.K., W.C. and K.N.; Supervision, K.N., Writing -original draft, K.K.; Writing -review & editing, K.N. All authors read and agreed to the published version of this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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