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Review Article

The Molecular Effects of Polyphenols on Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the main cause of irreversible blindness in the elderly. A healthy diet is considered one of the main modifiable factors for this disease. The consumption of fatty and high glycemic index foods is associated with a higher prevalence and incidence of AMD. Nonetheless, several studies have shown that the consumption of fruits, cereals and vegetables would help prevent or stabilize the progression of age-related macular degeneration. *In vitro* and *in vivo*, as well as populational studies, have demonstrated that polyphenols, with their antioxidant, anti-inflammatory, antiangiogenic and neuroprotective properties, have presented positive results in the prevention and/or control of AMD progression. Hence, this literature review aims to highlight the main polyphenols, described in experimental and/or populational studies, which have already been proven to be effective in reducing AMD progression and to present the protective molecular mechanisms, activated by these non-enzymatic antioxidants, which may potentially influence the progression of this disease.

Keywords: *Age-Related Macular Degeneration; Polyphenols; Phenolic Acids; Flavonoids; Stilbenes; Curcumin; Retinal Pigment Epithelium*

Abbreviations

AGEs: Advanced Glycation End Products; Akt: Proteins Kinase; AMD: Age-Related Macular Degeneration; AMPK: AMP-Activated Protein Kinase; AP-1: Activator Protein 1; ARE: Antioxidant Response Element; ARPE-19: Human Retinal Pigment Epithelial Cells; A2E: Pyridinium Bisretinoid; BAE: Blueberry Anthocyanin Extract; Bax: Bcl-2-Associated X Protein; Bcl-2: B-Cell Lymphoma-2; B-ext: Bilberry Extract; BM: Bruch's Membrane; CEP: Carboxyethylpyrrole; CG: Catechin Gallate; CNV: Choroidal Neovascularization; COX-2: Cyclooxygenase 2; CREB: Camp Response Element-Binding Protein; C3G: Cyanidin-3-Glucoside; Cur: Curcumin; CurDD: Curcumin Diethyl Disuccinate; DNA: Deoxyribonucleic Acid; DNMTs: DNA Methyltransferases; ECG: Epicatechin Gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin-3-Gallate; ERK: Extracellular Signal-Regulated Kinase; 8-OHdG: 8-Hydroxy-2'-Deoxyguanosine; 4-HNE: 4-Hydroxynonenal; GC: Gallocatechin; GCG: Gallocatechin Gallate; GSH: Glutathione; GSH-PX: Glutathione-Peroxidase; GST: Glutathione S-Transferase; LED: Light-Emitting Diode; L-ext: Lingonberry Extract; LINE-1: Long Interspersed Nuclear Element-1; HIF-1α: Hypoxia Inducible Fator-1α; HO-1: Heme Oxygenase 1; HUVEC: Human Umbilical Vein Endothelial Cells; H2O2: Hydrogen Peroxide; ICAM-1: Intercellular Adhesion Molecule-1; IL-1β: Interleukin-1β; IL-6: Interleukin-6; JNK: c-Jun N-Terminal Protein Kinase; LOX: Lipoxygenases; MAPK: Mitogen-Activated Protein Kinase;

MAP1LC3: Microtubule-Associated Protein Light Chain 3-II; MCP-1: Monocyte Chemoattractant Protein-1; MDA: Malondialdehyde; MMP-9: Matrix Metalloproteinases; MRPE: Mouse Retinal Pigment Epithelial; Mv: Malvidin; Mv-3-gal: Malvidin-3-Galactoside; Mv-3-glc: Malvidin-3-Glucoside; NQO1: NAD(P)H:Quinone Oxidoreductase; NF-κB: Nuclear Factor Kappa B; Nlrp3: NucleotideBinding Oligomerization Domain-Like Receptor Protein 3; Nox 1: Nadph Oxidase 1; Nrf2: Nuclear Factor E2-Related Factor 2; $O2^{-}$•: Superoxide; ONOO: Peroxynitrite; 1O2: Singlet Oxygen; OX-LDL: Oxidized Low-Density Lipoprotein; PEDF: Pigment-Epithelium-Derived Factor; Pkr: Double-Stranded RNA-Dependent Kinase; p42/p44: Mitogen-Activated Protein Kinases (MAPK, Also Called Erk2 And Erk1); RAGE: Receptor For Advanced Glycation End Products; ROS: Reactive Oxygen Species; RPE: Retinal Pigment Epithelium; Sal A: Salvianolic Acid A; SIRT1: Sirtuin 1; SOD: Superoxide Dismutase; TAC: Total Antioxidant Capacity; TNF- α: Tumor Necrosis Fator; TRX1: Thioredoxin; VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Receptor; XO: Xanthine Oxidase; w AMD: Wet Age-Related Macular Degeneration; ZO-1: Zonula Occludens-1

Introduction

Age-related macular degeneration is one of the main causes of irreversible blindness in the elderly [1]. The imbalance of the redox state has been regarded as the main triggering factor of this disease [2]. Such imbalance results in oxidation of important biomolecules [(lipids, proteins, carbohydrates, and deoxyribonucleic acid (DNA)] that promote increased expression of toxic molecules such as malondialdehyde (MDA), carboxyethylpyrrole (CEP), advanced glycation end products (AGEs), 4-hydroxynonenal (4-HNE), 8-Hydroxy-2'-deoxyguanosine (8-OHdG), which, among other alterations, promote the accumulation of lipofuscin inside the retinal pigment epithelium (RPE) cells [3]. This lipofuscin accumulation induces the dysfunction das RPE cells and causes a defective degradation of products derived from phagocytosis of the outer segments of photoreceptor cells, inducing pathological accumulation of lipids in Bruch's membrane (BM), and consequent damage to its permeability [4]. Besides affecting the metabolic exchanges of RPE cells with the choriocapillaris, the deposits of oxidized lipids on the BM activate the endothelial and RPE cells, promoting the attraction of immune system cells that release inflammatory cytokines, enzymes, and cell growth factors, responsible for the more advanced stages of the disease [5].

Among the AMD modifiable factors is the healthy diet [6]. It has been demonstrated that high intake of saturated fat and cholesterol was associated with an increased risk for early age-related maculopathy [7]. Nonetheless, several studies have suggested that the consumption of fruit and vegetables can contribute to the preservation of vision (8). Dietary polyphenols or phenolic compounds are non-enzymatic antioxidants representing a group of natural compounds that share common structural characteristics [9]. The beneficial effects of polyphenols to health have been associated with their antioxidant capacity. They remove most types of oxidant species by means of mechanisms that involve the transfer of an H-atom or a singlet electron to a stabilizing radical [10]. Additionally, most studies have demonstrated that polyphenols can form stable complexes with metallic ions, which may act as catalyzers in the production of oxidant species such as peroxide (H2O2), singlet oxygen (1O2), and peroxynitrite (ONOO-)] [11]. It has been accepted that polyphenols can scavenge reactive oxygen species (ROS) or increase the ability to neutralize ROS by inducing the expression of genes involved in cytoprotection, for example the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor. Nrf2 is a key regulator in the redox balance and signaling and regulates the expression of many antioxidant and detoxification genes by binding to antioxidant response elements (AREs), such as protein kinase C and nitric oxide synthases among other [12,13]. Polyphenols also regulate the nuclear transcription factors that modulating the synthesis of inflammatory mediators such as the cytokines tumor necrosis factor α (TNF- α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [14,15]. It is important to note that the actions of polyphenols can be potentiated when they are in synergism with other vitamins, such as vitamin E [16]. Several studies point to beneficial actions of polyphenols besides the antioxidant and anti-inflammatory effects, as cardiovascular, tumor suppressing, neuroprotective, analgesic, antipyretic, estrogenic, antimicrobial, antiviral properties, in the glucose metabolism, platelet function, endothelial function, blood pressure and cholesterol levels [16,17]. Regarding AMD, many experimental studies have reported the effectiveness of polyphenols in increasing the expression of antioxidized enzymes, inhibit the production of ROS and reduce several inflammatory markers [18-20]. Paradoxically, in some circumstances, polyphenols may become pro-oxidant and even reduce the absorption of antioxidants such as lutein [20,21], and potentially aggravate the AMD progression.

Considering AMD a disease that is triggered by the imbalance of the redox state, and consequent participation of cells and molecules associated with the oxidative stress and inflammation, it is possible to infer that polyphenols can potentially be part of the preventive and/or therapeutic approaches to treat AMD. In this regard this literature review aims to present the main polyphenols that have already shown in experimental and/or populational studies, to be effective in reducing AMD and to show the protective molecular mechanisms, activated by these non-enzymatic antioxidants, which can potentially influence the AMD progression. To meet this aim, this study will approach the following classes of polyphenols: phenolic acids, flavonoids, stilbenes, and curcumin

Methods of literature search

We searched publications in three electronic databases (Pubmed, MedlinePlus Health Information, and Elsevier Science) until November 2021. We used the following keywords and their synonyms in various combinations: age-related macular degeneration, polyphenols, phenolic acids, flavonoids, stilbenes, curcumin, oxidative stress, retinal pigment epithelium.

Phenolic acids

Phenolic acids are a class of non-flavonoid phenolic compounds formed by a carboxylic acid group. They can be divided into two types, benzoic acid and cinnamic acid derivatives, and are found in a variety of plant-based foods. Seeds, fruit skins and vegetable leaves contain them in higher concentrations [22,23]. Hydroxybenzoic acids form complex structures such as hydrolyzable tannin found in some fruits such as mango (gallotannin) and red fruits (ellagitannin) [24]. Hydroxycinnamic acids, in turn, are more common in human diets and primarily consist of p-coumaric (para-coumaric), caffeic, ferulic, and sinapic acids. Caffeic acid is one of the most abundant and one of the most found hydroxycinnamc acids in many fruits, mainly on the outermost part of ripe fruits. Ferulic acid is largely found in grains and cereals, and generally, more concentrated on the outermost part [24]. The molecular structure of each group of phenolic acids is given in figure 1. The salvianolic acid A (Sal A) (Dan Phenolic Acid A), (R)-3- (3,4-Dihydroxyphenyl)-2-hydroxypropanoic acid, is an active monomer extracted from *Salvia miltiorrhiza* Bunge (Danshen), a traditional Chinese medicine, known to protect RPE from lipid oxidative damage and chronic inflammation through up-regulating the Nrf2 and inactivating the purinergic 2X7 receptor-double-stranded RNA-dependent kinase-Nucleotidebinding oligomerization domain-like receptor protein 3 (P2x7r-Pkr-Nlrp3) signaling pathway [25]. Sal A also inhibits oxidized low-density lipoprotein (OX-LDL) effects on exacerbating choroidal neovascularization via downregulating cylindromatosis (a tumor suppressor) [26].

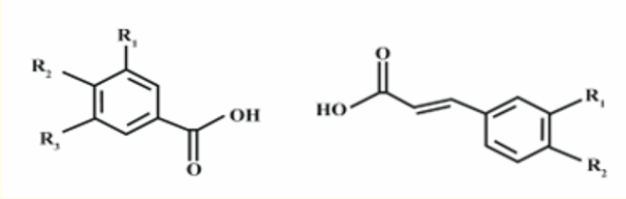

Figure 1: *The molecular structure of each group of phenolic acids.*

Flavonoids

Flavonoids are of phenolic nature, a group of structurally diverse natural or synthetic compounds that present a basic structure formed by C6-C3-C6 and may exhibit biological activity [27]. The basic structure of flavonoids is shown in figure 2. Flavonoids remove superox-

ide ions and hydroxil radicals and "donate" a hydrogen atom to the peroxyl radical, forming the flavonoid radical. They also chelate the participant metals of the Fenton reaction, which produces ROS [27-29]. Additionally, they suppress the expression of pro-inflammatory genes and molecules that contribute to retinal degeneration. This anti-inflammatory action of flavonoids can be observed in the retina of Abca4-/- and Rdh8-/- mice that were exposed to bright light [30]. Flavonoids are also involved in sensory transduction of the visual system and visual pigment regeneration, thus making them viable drug candidates. Studies have shown that foods rich in flavonoids attenuate oxidative stress and promote vision improvement in certain eye pathologies [31]. A population-based cohort study, with 2856 adults aged ≥ 49 y at baseline and 2037 followed up 15 years later, demonstrated that dietary intake of flavonoids reduced the odds of the prevalence of any AMD [32]. A study with 494 participants with wet age-related macular degeneration (wAMD), after 12 months of anti-vascular endothelial growth factor (anti-VEGF) therapy, reported that higher intakes of dietary flavonoids, specifically flavanols and flavan-3-ols, could be associated with better long-term treatment outcomes in neovascular AMD (nAMD) patients receiving anti-VEGF therapy [33]. A systematic review and meta-analysis concluded that flavonoids flavonoids have the potential to become anti-angiogenic agents [34]. Despite being antioxidants, flavonoids may have prooxidant actions, causing oxidative stress [21].

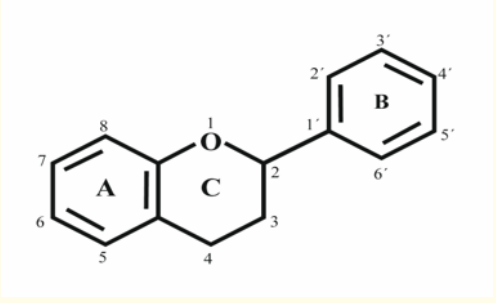

Figure 2: *Basic structure of flavonoids.*

Among the flavonoids, the following sub-classes are presented: isoflavones, flavones, flavanols, flavanones, chalcones, flavanols, proanthocyanidins, anthocyanidins and anthocyanins.

Isoflavones

While most flavonoids have the B-ring attached at Carbon 2 of C ring, isoflavones have the B-ring attached at the C3 of C-ring [9]. Their structure, classified as phytoestrogen, is similar to that of the estrogen and may attach to receptors of this hormone [35]. Genistein, 40,5,7-trihydroxyisoflavone, and daidzein, 40,7-dihydroxyisoflavone, are the most common isoflavones. They are mainly found in the legume family, soybeans representing a major source [36]. Genistein, a nonselective tyrosine kinase inhibitor [37], significantly reduced the protein level of monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and matrix metalloproteinase-9 (MMP-9) in the RPE-choroid complex and suppressed the expression levels of Ets-1 and F4/80, thus indicating its anti-angiogenic property during choroidal neovascularization (CNV) [38]. Another study revealed partial inhibitory effects on laser-induced CNV mouse model of genistein compared to specific inhibitors of VEGF/Pigment-epithelium-derived factor (PEDF) receptor kinases [39]. P. lobata extract and its individual constituent compounds (puerarin, daidzein and daidzin) reduced oxidative stress, preserved zonula occludens-1 (ZO-1) and inhibited membrane permeability in H2O2-treated human retinal pigment epithelial cells (ARPE-19). Additionally, H_2O_2-induced p38 MAPK and JNK phosphorylation was reduced after treatment of RPE cells with the *P. lobata* extract [40]. Therefore, P. lobata extract may play a preventive role in AMD by attenuating oxidative stress [40].

Flavones

Flavones can be found in many fruits, vegetables, and beverages. They are found as both *O*- and *C*-glycosides in their native forms [41]. These consist basically of glycosides of luteolin, apigenin and chrysin [41].

Luteolin

3',4',5,7-tetrahydroxyflavone, is a flavonoid polyphenolic compound found in celery, carrots, broccoli, peppers, apples, mangoes, blueberries, peaches, plums, chrysanthemum flowers, *Taraxacum mongolicum*, among others [42,43]. The luteolin protected ARPE-19 cells from IL-1β-stimulated increases of IL-6, IL-8, sICAM-1, and MCP-1 production by blocking the activation of MAPK and nuclear factor kappa B (NF-κB) signaling pathways, thus ameliorating the inflammatory response [43]. Similarly, another study demonstrated that luteolin reduced the release of inflammatory cytokines, protecting ARPE-19 cells from oxidative stress-induced death. This reduction in inflammatory markers was related to reduced activation of MAPKs and cAMP response element binding protein (CREB), without the participation of NF-κB or Sirtuin 1 (SIRT1) [44]. However, although luteolin reduces inflammation, it can cause DNA damage leading to toxicity in ARPE-19 cells [45]. Cynaroside (luteolin 7-glycoside) attenuated the decrease in the activity of cells subjected to oxidative stress. It acted on biomarkers of intracellular ROS level, decreasing malondialdehyde (MDA) level, and increasing the expression of glutathione (GSH), superoxide dismutase (SOD), and catalase. Furthermore, cynaroside protected ARPE-19 cells from apoptosis by down-regulating caspase-3 protein activation which was controlled by the upstream proteins Bcl-2 (B-cell lymphoma protein 2) and Bcl-2-associated X protein (Bax). In this study, it was also shown that cynaroside promotes the expression of phosphorylated Akt (p-Akt), contributing to the antioxidant and antiapoptotic effects [46]. In addition to alleviating apoptosis, cinnaroside was able to induce autophagy *in vitro* and in vivo, protecting the blue light-induced retinal degeneration [47].

Apigenin

4',5,7-trihydroxyflavone, is a natural product belonging to the flavone class [48]. Apigenin can be found in a variety of vegetables, herbs and fruits. Spinach, parsley, celery and dried oregano are also dietary sources with high apigenin content [48]. Apigenin up-regulated the expression of antioxidant enzymes via the Nrf2 pathway and up-regulated autophagy, inhibiting retinal oxidative damage in the retina of a mouse model with dry AMD [49].). Treatment with apigenin-7-diglucuronide protected photoreceptors in BALB/c mice exposed to bright light. It attenuated photoreceptor apoptosis, reduced oxidative stress, suppressed reactive gliosis and microglial activation, and inhibited the expression of pro-inflammatory genes in retinas subjected to oxidative stress (50). In an experimental model of wAMD, apigenin inhibited the development of CNV, interfered with the proliferation and migration of endothelial cells, reduced the growth of human umbilical vein endothelial cells (HUVEC) and choroidal endothelial cells, and inhibited the migration of HUVEC for further of 50% in relation to the control. In this regard, apigenin attenuated choroidal angiogenesis *in vitro* and *in vivo* [51].

Chrysin

5,7-dihydroxyflavone, a natural flavonoid found in high concentrations in honey and propolis, presents anti-inflammatory, anti-oxidative, and anti-angiogenic properties, showed an inhibitory effect on CNV in an experimental rat model [52]. Corroborating this finding, intravitreally injected chrysin inhibited induced laser-induced CNV, in Brown Norway rats, and downregulated hypoxia inducible fator-1α

(HIF-1α) and VEGF expression [53]. Nevertheless, chrysin demonstrated cellular toxicity and caused inhibition of DNA synthesis at low concentrations in normal trout liver cell lines [54].

Flavonol

Quercetin and kaempferol are flavonoid aglycones that usually concentrate in the outermost layers of plants and fruits, such as shells and leaves, and are likely to reduce AMD progression [9,24,55,56].

Quercetin

3,3',4',5,7-pentahydroxyflavone, is a flavonoid found in lettuce, pepper, onion, black chokeberry, tomato, broccoli, tea, onion, and apple [57]. These sources account for an estimated dietary intake of quercetin of 5 to 40 mg/day. However, the main concern associated with the consumption of quercetin is its generally poor oral bioavailability [58]. The use of 50 to 150 mg per day of quercetin significantly increased plasma concentrations of quercetin by between 178% and 570%. This significant increase of quercetin plasma concentrations was not sufficient to modify the concentrations of plasma α - and γ-tocopherols, serum uric acid, TNF-α, OX-LDL, or plasma antioxidative capacity. It was also observed that quercetin did not significantly modify serum lipids and lipoproteins, body composition and resting energy expenditure. In this context, it can be concluded that the biological activity of dietary quercetin is not sufficient to reach adequate plasma levels, since it is necessary to have a minimum dose to produce significant effects in *in vitro* assays [59]. However, in *in vitro* studies quercetin presented a powerful antioxidant effect, combining with free radical species to form less reactive phenoxy radicals, scavenging DPPH radical, inducing lipid peroxidation inhibition [60], and inhibiting XO and lipoxygenases (LOX) [61]. In ARPE-19 cells, quercetin inhibited pro-inflammatory molecules and attenuated apoptosis. On the other hand, suppression of the inflammatory and apoptosis pathways in the eye was not sufficient to improve the retinal AMD-like lesions in the Ccl2(-/-)/Cx3cr1(-/-) mice [55]. Another *in vitro* study, analyzing retinal photoreceptor cells, demonstrated the good performance of quercetin in attenuating the inflammatory response by inactivation of NF-κB signals through inhibition of MAPKs and Akt [62]. Additionally, quercetin protected ARPE 19 cells subjected to oxidative stress by activating the Nrf2 pathway, inhibiting endoplasmic reticulum (ER) stress, targeting antiapoptotic proteins [18], and by reducing mitochondrial function [63]. Corroborating these studies, quercetin has been shown to attenuate light-induced retinal oxidative and inflammatory effects [64].

Kaempferol

3,4',5,7-Tetrahydroxyflavone, can be found in many plants like vegetables, fruits and beans. Traditional medicinal herbs such as *Chrysanthemum, Astragalus mongholicus*, ginkgo leaf and dried raspberry are also sources of this flavonoid subclass [65]. Kaempferol has been shown to be a potent superoxide scavenger, protecting ARPE-19 cells from H_2O_2-induced oxidative stress and apoptosis through the signaling pathways involving Bax/Bcl-2 and caspase-3 molecules [56]. In H_2O_2-treated ARPE-19 cells, kaempferol inhibited VEGF mRNA expression levels and attenuated oxidation by regulating both ROS and SOD activities [56]. Additionally, kaempferol attenuated sodium iodate-induced retinal degeneration, as well as inhibited retinal cell apoptosis and upregulated VEGF protein expression in RPE cells. This study showed that the total antioxidant capacity (TAC) of kaempferol is approximately two times stronger than that of lutein, another non-enzymatic antioxidant used in the prevention of AMD [56].

Flavanones

Flavanones, 2,3-Dihydroflavone, are found in citric fruits such as orange and tangerine [66]. Hesperetin is a flavanone glycoside compound that presents anti-inflammatory and antioxidant effects. In ARPE-19 cells submitted to oxidative stress induced by H_2O_2, hesperetin inhibited cellular apoptosis, ROS overproduction and MDA formation as well as enhanced the SOD and GSH levels. It is believed that the underlying mechanisms may be related to the activation of the signaling pathway Keap1-Nrf2/Heme oxygenase 1 (HO-1) [67].

Chalcones

Chalcones, *trans*-1,3-diaryl-2-propen-1-ones, are characterized by presenting a central enones system with two lateral aromatic rings, easily found in some plants such as hops and licorice, in fruits such as apple [68]. A novel chalcone analogue, 1-(2,3,4-trimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-acrylketone (Tak), a Nrf2 activator, protected ARPE-19 cells against oxidative stress-induced death and mitochondrial dysfunction [69].

Flavanols

Flavanols, flavan-3-ols, and their derivatives [gallocatechin (GC), catechin gallate (CG), gallocatechin gallate (GCG), epigallocatechin (EGC), epicatechin gallate (ECG), epigallocatechin-3-gallate (EGCG)] are present in green tea, red wine, cocoa, grape seeds, berries, cranberries, cinnamon bark, sorghum grains, chokeberries, hazelnuts, pears, blueberries, and apples [9,70]. Flavanols are potent antioxidants, known for scavenging free radicals *in vitro* and *in vivo* [70]. EGCG decreases ROS production through the inhibition of prohibitin1, which regulates ER-mitochondrial the site, restoring $[Ca^{2+}]_i$ homeostasis and inhibiting apoptosis [71]. EGCG was approximately 10 times more potent than trolox (vitamin E analogue) at attenuating lipid peroxidation caused by the nitric oxide donor, sodium nitroprusside, on brain membranes [72]. It has been demonstrated that EGCG pretreatment protected primary rat RPE cells from H_2O_2-induced death [73]. It was also shown that EGCG inhibited UVA-induced H_2O_2 production, reducing MAPK activation, and expression of Cyclooxygenase 2 (COX-2). Moreover, it enhanced RPE cell survival after UVA exposure [74]. EGCG played a regulatory role in UVB irradiation-induced autophagy in RPE cells, leading to a significant inhibition in the formation of microtubule-associated protein light chain 3-II (MAP1LC3) and autophagosomes. EGCG reduced the ROS generation and apoptosis in ARPE19 cells, and partially blocked the decreased phosphorylation of JNK1 and c-Jun, attenuating the damage induced by the oxidative stress caused by UVB irradiation [75]. ARPE-19 cells exposed to 12-O-tetradecanoylphorbol-13-acetate and TNF-α significantly reduced MMP-9 mRNA and protein expression levels when treated with EGCG. In addition to inhibiting cell death, there was attenuation of mRNA expressions of key angiogenic factors (MMP-9, VEGF, VEGF Receptor-2) by reducing the generation of ROS. Consequently, a significant reduction in proliferation, vascular permeability, and tube formation in human retinal microvascular endothelial cells was observed. This study demonstrated *in vivo* that EGCG attenuated the breakdown of the blood-retinal barrier, significantly reducing vascular leakage and permeability [76]. It downregulated 78-kDa glucose-regulated protein (GRP78), C/EBP homologous protein (CHOP), PKR-like ER kinase (PERK), endoplasmic reticulum disulphide oxidase 1 α (ERO-1 α), inositol-requiring enzyme α (IRE- α), cleaved polymerase (PARP), cleaved caspase 3 (ASP 175), caspase 12 and upregulated expression of calnexinin mouse retinal pigment epithelial (MRPE) cells. The expression of AktB, phosphatase and tensin homolog and GSK3β also confirmed that EGCG exerts an inhibitory effect on apoptosis on MRPE cells. There was upregulation in the phosphorylation of Akt at ser473, phospho ser380 of phosphatase, and tensin homolog, as well as increase in Akt activity. On the other hand, phosphorylation at ser9 of GSK3β was inhibited [77]. A prodrug of EGCG (pro-EGCG) alleviated mouse laser-induced CNV leakage and reduced CNV area by down-regulating HIF-1α/VEGF/VEGFR2 pathway, M1-type macrophage/microglia polarization, as well as endothelial cell viability, proliferation, migration and tube formation, indicating a novel potential therapy for AMD [78].

Proanthocyanidins

Catechin and epicatechin monomers may form oligomers and polymers, and produce proanthocyanidins, also known as condensed tannins [9,79]. The proanthocyanidins, polyhydroxyflavan-3-ol, are plant flavonoids commonly found in our daily diet. They can be found in grains such as rice, wheat, barley, sorghum, corn, buckwheat and some forage grasses. It is still poorly understood how these biological effects are exerted, given that the bioavailability of proanthocyanidins is very low [80]. However, in experimental studies, proanthocyanidins have shown to exert important antioxidative effects. ARPE-19 cells exposed to blue light were protected by proanthocyanidins contained in the cranberry juice fraction, thus exhibiting good free radicals scavenging activity (81). Oral administration of the fraction of polyphenolic compounds from the seed shells of Japanese horse chestnut (*Aesculus turbinata* BLUME) significantly suppressed the decrease in electroretinogram amplitudes and the thickness of the outer nuclear layer of albino rats exposed to light, as well as induced the

elevation of the antioxidant activity, and the suppression of the lipid oxidation of the retina. Therefore, this proanthocyanidin protected the retina by inhibiting oxidative stress and apoptotic mechanisms [82].

Anthocyanidins

Anthocyanidins or aglycones are polyphenols that may be produced from the depolarization of proanthocyanidins, exerted by the action of acids. The basic chemical structure is 2-phenyl-1-benzopyrilium, which links hydroxyl (-OH) and/or methoxyl (-OCH_3) groups, and no sugars are attached to the side groups of flavylium ion [9,79]. They compose the red, blue, and purple pigments in the petals of flowers, fruits, vegetables, and grains such as black rice [83]. Among the most found anthocyanidins, the ones that stand out are cyanidin, delphinidin and pelargonidin [84]. Their structural characteristics make it highly reactive to ROS [84]. In ARPE-19 cells undergoing H_2O_2, delphinidin was effective in increasing cell viability and reducing the apoptosis of ARPE-19 cells. Furthermore, delphinidin significantly inhibited the intracellular oxidative stress and expression of the protein NADPH Oxidase 1 (Nox1). In addition, delphinidin inhibited MDA formation as well as enhanced the SOD, catalase, and glutathione-peroxidase (GSH-PX) levels, which were regulated by increasing nuclear Nrf2 protein expression [85]. Another study demonstrated that the pre-treatment with cyanidin-3-O-glucoside (C3G) associated with a delphinidin-3-O-glucoside, lutein and zeaxanthin, attenuated the damage in ARPE-19 cells caused by the exposure to UVB irradiation [86].

Anthocyanins

The chemical structure of anthocyanins is flavylium cation (2-phenyl-1-benzopyrilium), which links hydroxyl (-OH) and/or methoxyl (-OCH3) groups, and one or more sugars. They are compounds formed by the grouping of sugar, an aglycone (anthocyanin) and conditionally, some acids [87]. The oxidative cleavage of proanthocyanidins can yield anthocyanins [87]. Anthocyanin pigments that range from red to purple and blue are responsible for the attractive colors of many flowers, fruits and vegetables, such as grape skins, blueberries and black raspberries [87]. Regarding the redox mechanism, bilberry extract (B-ext) and lingonberry extract (L-ext) extracts, which contain large amounts of polyphenols such as anthocyanins, resveratrol and proanthocyanidins, attenuated the damage to the retinal photoreceptor cell induced by the blue light diode (LED). It was also observed that these polyphenols improved the viability of 661 W cells, inhibited the activation of p38 MAPK and NF-κB as well as the generation of intracellular ROS. Finally, B-ext and L-ext inhibited caspase-3/7 activation and autophagy [88]. Corroborating these findings, the content of anthocyanins present in the maqui berry extract was found to exert a protective role to the retina cells against the light-induced degeneration of photoreceptors [89]. The photooxidation of the pyridinium bisretinoid (A2E) molecule in RPE cells was inhibited by anthocyanins from blackcurrant and blueberry extracts [90]. In ARPE-19 cells treated with H2O2, blueberry anthocyanin extract, malvidin (Mv), malvidin-3-glycoside (Mv-3-glc) and malvidin-3-galactoside (Mv-3-gal) reduced oxidative stress, decreasing the levels of ROS and MDA, and increasing the levels of SOD, catalase and GSH-PX. blueberry anthocyanin extract and the anthocyanin standards improved cell viability and significantly inhibited cell apoptosis. Mitogen-activated-protein-kinase pathways, including extracellular signal-regulated kinase (ERK)1/2 and p38, were involved in the bioactivities. The reduction of VEGF levels and the activation of Akt-signal pathways were also attributed to anthocyanins [91]. Blueberry extract acted on certain apoptotic proteins, such as Bax, Bcl-2, and caspase-3, attenuating the changes caused by light in the retinal cells of pigmented rabbits. It was also observed that blueberry extract caused an increase in the levels of SOD, GSH-PX, catalase and TAC, as well as a reduction in the level of MDA. Additionally, blueberry extract inhibited the elevation of levels of proinflammatory cytokines and growth factors (IL-1β and VEGF) [92]. It was suggested that signal transduction pathways are stimulated by anthocyanins and other phenolics from bilberry, influencing genes controlled by the ARE, upregulating the oxidative stress defense enzymes HO-1 and glutathione S-transferase-pi (GST-pi) in RPE [93]. Another important anthocyanin, C3G, reduced the formation of photooxidized A2E species, decreasing the formation of methylglyoxal adducts in the cells, and inhibiting the expression of mRNA encoding receptor for AGEs. It also protected glutathione from reacting with photooxidized A2E. Cyanidin-3-glucoside inhibited the release of the lipid peroxidation product 4-HNE in rod outer segments incubated with all-trans-retinal to generate bisretinoid [64]. In ARPE-19 cells exposed to 4-HNE and treated with C3G, there was a decrease in the rate of cellular apoptosis, potent inhibitory effects on Nlrp3 inflammasome activation, delay and decrease in JNK activation and suppres-

sion in the transcriptional activity of activation protein (AP)-1 [94]. It is important to point out that bilberry extracts containing anthocyanins have become rather popular among patients with AMD in Switzerland as a medication for primary or secondary prophylaxis [95].

Stilbenes

The Stilbe family is a group of compounds consisting of 2 aromatic rings joined by a methylene bridge. The molecular structure of stilbenes is given in figure 3. The main representative of this group is resveratrol (trans-3,40,5-trihydroxystilbene). This polyphenol is mainly found in grape seed and skin [96], as well as in blackberries, blueberries, cranberries, peanuts, peanut shells and peanut butter, among other fruits or vegetables [58]. Resveratrol interacts with numerous molecular targets, especially COX-2, SIRT1, transcription factors, cytokines transcription factors, and cytokines [96]. Regarding the molecular targets in RPE cells, many studies have been published reporting several interactions with this polyphenol. In ARPE-19 cells treated with H2O2, resveratrol significantly reduced the cell proliferation, inhibited intracellular oxidation, and protected RPE cells from death. It is important to note that attenuation in cell proliferation was associated with an inhibition of MAPK and extracellular signal-regulated kinase (ERK 1/2) activities [97]. Further studies revealed that resveratrol protected ARPE-19 cells from acrolein-induced damage (98), attenuated the cytotoxic, oxidative, inflammatory and/or angiogenic activities [99-103], improved a cell viability in AMD transmitochondrial cell lines [104], and suppressed intracellular H2O2 generation induced by UVA irradiation in RPE cells. Additionally, resveratrol also decreased extracellular signal-regulated kinase activation, JNK and p38 kinase. Furthermore, resveratrol could also reduce UVA-induced COX-2 expression in RPE cells [19]. It decreased the damages on ARPE-19 cells undergoing treatment with A2E followed by the exposure to blue light, confirming the protective effect of resveratrol on these cells [105]. Activation of PPARα and alteration of PPARδ conformation is one of the possible mechanisms attributed to resveratrol for the protection of RPE cells [106]. It has also been reported that a treatment with resveratrol in ARPE-19 cells, under oxidative and inflammatory conditions, neutralized the harmful effect in the DNA methyltransferases and SIRT1 and methylation da LINE-1 functions [107]. It is known that SIRT1 may mediate, at least in part, the hypoxia inducible factor (HIF)-1α and the secretion of VEGF in RPE and endothelial cells, which can potentially trigger CNV [108]. Hence, activation of SIRT1 represents an important molecular protective mechanism promoted by resveratrol. It is relevant to point out that SIRT1 is located in the nucleus and cytoplasm of cells forming all normal ocular structures, such as the cornea, lens, iris, ciliary body, and retina, providing protection against diseases related to oxidative stress-induced ocular damage [109]. Resveratrol also protected RPE cells against the oxidative damage by modulating SOD and MDA activity and activating Bcl-2 expression [110]. Another important finding regarding resveratrol is that it induced a significant increase of SOD, GSH-PX, GSH, and catalase activities under oxidative stress conditions [111]. The increase in the expression of antioxidant enzymes in RPE cells, promoted by resveratrol, could also be observed in another study that reported that this polyphenol can improve hydroquinone (HQ)-induced toxicity in RPE cells by improving the mitochondrial bioenergetics, upregulating antioxidant genes HO-1, and stimulating unfolded protein response [112]. In ARPE-19 cells exposed to acrolein, resveratrol exerted protection against cytotoxicity via increases in the mitochondrial bioenergetics. In addition, the antioxidant action of resveratrol attenuated laser-induced CNV in animals exposed to cigarette smoke [113]. Resvega, containing trans-resveratrol and omega-3 fatty acids, among other nutrients, could induce autophagy and provide cytoprotection in ARPE-19 cells that were treated with autophagy inhibitor bafilomycin A1 or proteasome inhibitor [114]. Resveratrol was able to induce a specific anti-inflammatory response and autophagy in ARPE-19 cells, significantly reducing the mortality rate of these cells [115]. In regard to wAMD, among several molecular mechanisms that try to explain resveratrol antiangiogenic action, are the activation of the stress-activated protein kinase (SAPK)/JNK pathway [116], the activation of SIRT1 [108], the decrease in VEGF-R2 expression [117], the inhibition of the production of CXCL11, CXCL9, CCL2 and CCL5 induced by pro-inflammatory cytokines, as well as the partial blockage of NF-κB activation [118]. A study carried out on ARPE-19 cells treated with various combinations of BEV (bevacizumab) and resveratrol, revealed a partial decrease in the secreted VEGF levels when compared to untreated controls. Cultures treated with BEV + resveratrol showed lower epithelial-mesenchymal transition compared to cultures treated with BEV. However, the proliferation status was similar in BEV both groups [119]. Therefore, the use of resveratrol to help in the antiangiogenic therapy should be considered. A randomized trial in patients with unilateral wAMD prescribed the original Age-Related Eye Disease group (AREDS) formulation (control group) and a product that adds docosahexaenoic acid (DHA), lutein, zeaxanthin, resveratrol, and hydroxytyrosol to the formula (intervention group). At the end of the study, at month 12, there was no significant difference in visual acuity between the groups

[120]. Nevertheless, a study involving three patients with AMD showed that ocular structure and activity were enhanced, suggesting that resveratrol may be effective in treating AMD [121].

Curcumin

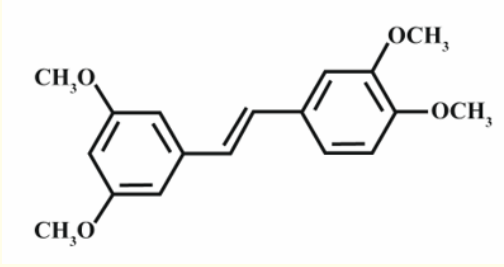

Figure 3: *The molecular structure of stilbenes.*

Curcumin, diferuloylmethane; 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is the orange pigment extracted from turmeric, the rhizome of *Curcuma longa* [122]. The molecular structure of curcumin is provided in figure 4. Curcuminoids are recognized by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" [123]. This safety profile has been demonstrated by clinical trials, even at doses between 4,000 and 8,000 mg/day, or even higher [123]. However, their safety and therapeutic efficacy were not enough to be considered drugs yet. Curcumin is hydrophobic, showing low systemic bioavailability [123,124]. It has been shown that both curcumin as well as its metabolites promote scavenging of DPPH, hydroxyl radicals, nitric oxide and superoxide anions [125], and activate the antioxidant enzymes such as GSH-PX, glutathione S-transferase (GST) and nicotinamide adenine dinucleotide phosphate (NADPH):quinone reductase [126]. In a rat model of light-induced retinal degeneration and in retina-derived cell lines, curcumin inhibited cellular inflammatory responses and protected cells, modulating the expression and activation of many cellular regulatory proteins such as NF-κB, Nrf2, and growth factors [127]. Curcumin treatment regulated proliferation, oxidative stress and apoptosis on RPE cells aged by exposure to oxidative stress [128-130]. In an ARPE-19 cell line subjected to acrolein, a curcumin analog, 1, 5-bis (2-trifluoromethylphenyl)-1, 4-pentadien-3-one (C3), played a protective effect against cellular oxidative damage and preserved GSH levels and mitochondrial function. C3 displayed a more efficient protective effect than curcumin. C3 and curcumin induced Nrf2 nuclear translocation and Nrf2 target transcription genes, and both activated the PI3/Akt pathway [131]. Similarly, curcumin reduced ROS levels and played a protective role on patient-derived RPEs with the AMD-associated background (AMD-RPEs) treated with H2O2. In addition, genes that regulate oxidative stress such as PDGF, VEGF, IGFBP-2, HO-1, SOD-2 and GSH-PX had their expressions also modulated by curcumin [132]. Corroborating these studies, both the prodrug curcumin diethyl disuccinate (CurDD) and curcumin protected ARPE-19 cells from oxidative stress-induced death through the modulation of p44/42 (ERK) and the involvement of downstream molecules Bax and Bcl-2. Cells treated with CurDD and curcumin also showed increased expression of the antioxidant enzymes HO-1 and NAD(P)H:quinone oxidoreductase (NQO1). As for the performance in the attenuation of oxidative stress, a greater effectiveness of CurDD was observed in relation to the original drug in all cases. This study revealed that the characteristic curcumin low solubility and bioavailability may be mitigated when used as pro-drug (CurDD) [133]. In addition, it was observed that patients with nAMD, treated with intravitreal injections of anti-VEGF (IVIs) plus oral administration of a curcumin-based nutritional supplement, significantly improved best-corrected median visual acuity compared to controls (treated with only IVs). However, there was no statistical difference in central macular thickness between the groups. It is important to point out that the treated group received fewer injections compared to controls [134].

Conclusion

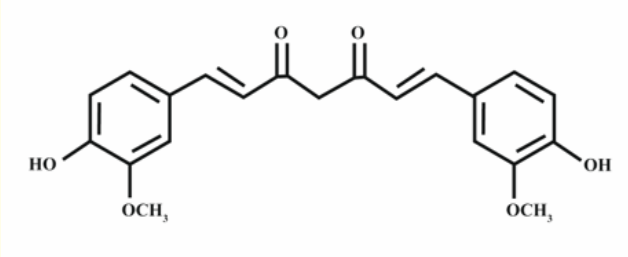

Figure 4: *The molecular structure of curcumin.*

Studies carried out *in vitro* and *in vivo*, using RPE cells, reproduced the studies completed in other cell types (Table 1-3). It was confirmed that the polyphenols affect multiple molecular targets and intracellular signaling layers, acting as modulators of the gene expression and signaling pathways related to the cell function and protection such as AKT, antioxidant response element, caspases, SIRT 1 e PPAR. Polyphenols also inhibit the expression and activation of many cellular regulatory proteins such as NF-κB, COX-2, NLRP3 inflammasome, MAPK, growth factors, among others. In this regard, polyphenols inhibit the inflammatory mediators such as the cytokines tumor necrosis factor α, interleukin-1β, and interleukin-6, chemiotactic molecules such as MCP-1, and adhesion molecules such as ICAM-1. These protective molecular mechanisms induced by polyphenols can reduce the apoptosis in ARPE19 cells, inhibit proliferation, vascular permeability, tube formation in VEGF-induced human retinal microvascular endothelial cells (HRMECs), alleviate laser-induced CNV leakage and reduce the CNV area. Comparatively, the number of populational studies in relation to experimental studies is very small. The low oral bioavailability and the difficulty to determine the quantities of vegetables and fruits that should be consumed to obtain an adequate supply of these nutrients and consequently attain the preventive and/therapeutic effects in AMD, may account for this difference. Nevertheless, the proven antioxidant, anti-inflammatory, antiangiogenic and neuroprotective properties identified at laboratory level reveal the great potential of polyphenols to integrate the group of molecules to be used in the AMD prevention and/or treatment.

Polyphenols		Up-regulate	References	Inhibit	References
Phenolic acids	Sal A	Nrf2	Mao., *et al*. [25]	P2x7r-Pkr-Nlrp3 OX-LDL	Mao., *et al*. [25] Mao., *et al*. [25]; Mao., *et al*. [26]
	Isoflavones			MCP-1 ICAM-1 MMP-9 Ets-1 F4/80 ROS Disruption of ZO-1 MAPK [JNK / p38]	Kinoshita., *et al*. [38] Kinoshita., *et al*. [38] Kinoshita., *et al*. [38] Kinoshita., *et al*. [38] Kinoshita., *et al*. [38] Kang., *et al*. [40] Kang., *et al*. [40] Kang., *et al*. [40]

	Flavones	GSH SOD Catalase Bcl-2 Akt phosphory-lation Autophagy Nrf2	Yu., *et al.* [46] Yu., *et al.* [46] Yu., *et al.* [46] Yu., *et al.* [46] Yu., *et al.* [46] Feng *et al* [47]; Zhang *et al* [49] Zhang *et al* [49]	IL-6 IL-8 MAPK NF-κB CREB ROS MDA Caspase-3 Bax HUVEC HIF-1α VEGF	Huang., *et al.* [43] Huang., *et al.* [43] Huang., *et al.* [43]; Hytti,*et al* [44] Huang., *et al.* [43] Hytti,*et al* [44] Yu., *et al.* [46] Yu., *et al.* [46] Yu., *et al.* [46] Yu., *et al.* [46] Zou., *et al.* [51] Song., *et al.* [53] Song., *et al.* [53]
Flavo-noids	Flavonols	Nrf2 SOD Catalase Bcl-2	Weng., *et al.* [18] Du., *et al.* [56] Du., *et al.* [56] Du., *et al.* [56]	NF-κB MAPKs Akt phosphorylation A2E RAGE 4-HNE Bax Caspase-3 VEGF ROS	Lee., *et al.* [62] Lee., *et al.* [62] Lee., *et al.* [62] Wang., *et al.* [64] Wang., *et al.* [64] Wang., *et al.* [64] Du., *et al.* [56] Du., *et al.* [56] Du., *et al.* [56] Du., *et al.* [56]
	Flavanones	SOD GSH Nrf2/HO-1	Zhu., *et al.* [67] Zhu., *et al.* [67] Zhu., *et al.* [67]	ROS MDA	Zhu., *et al.* [67] Zhu., *et al.* [67]

Table 1: *Molecular effects of polyphenols.*

Polyphenols		Up-regulate	References	Inhibit	References
Flavonoids	Chalcones	Nrf2	Cui., *et al.* [69]		
	Flavanols	Autophagy Calnexinin Akt phosphorylation Ser380/Tensin	Cao., *et al.* [75] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77]	MAPK COX-2 MAP1LC3 ROS JNK MMP-9 TNF-α VEGF VEGFR-2 GRP78 CHOP PERK ERO-1 α IRE- α PARP ASP 175 Caspase 3 and 12 Phosphorylation Ser 9-GSK3β HIF-1α	Chan., *et al.* [74] Chan., *et al.* [74] Cao., *et al.* [75] Cao., *et al.* [75], Lee., *et al.* [76] Cao., *et al.* [75] Lee., *et al.* [76] Lee., *et al.* [76] Lee., *et al.* [76], Xu., *et al.* [78] Lee., *et al.* [76], Xu., *et al.* [78] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Karthikeyan., *et al.* [77] Xu., *et al.* [78]
	Proanthocyani-dins			ROS	Ishihara., *et al.* [82]
	Anthocyanidins	Nrf2 SOD Catalase GSH-PX	Ni., *et al.* [85] Ni., *et al.* [85] Ni., *et al.* [85] Ni., *et al.* [85]	ROS Nox1 MDA MAPKs [JNK/ p38]	Ni., *et al.* [85] Ni., *et al.* [85] Ni., *et al.* [85] Silván., *et al.* [86]

	Anthocyanins	SOD Catalase GSH-PX Akt phosphorylation TAC HO-1 GST-Pi Bcl-2	Huang., *et al*. [91]; Wang., *et al*. [92] Huang., *et al*. [91]; Wang., *et al*. [92] Huang., *et al*. [91]; Wang., *et al*. [92] Huang., *et al*. [91] Wang., *et al*. [92] Milbury *et al* [93] Milbury *et al* [93] Wang., *et al*. [92]	AGEs 4-HNE ROS MAPK [p38] NF-κB Caspase-3/7 A2E ROS MDA VEGF Bax Caspase-3 IL-1β VEGF Nlrp3 JNK activation Ap-1	Wang., *et al*. [64] Wang., *et al*. [64] Ogawa *et al* [88] Ogawa *et al* [88]; Tanaka *et al* [89] Ogawa *et al* [88] Ogawa *et al* [88] Jang., *et al*. [90]; Wang., *et al*. [64] Tanaka., *et al*. [89], Huang., *et al*. [91]; Huang., *et al*. [91]; Wang., *et al*. [92] Huang., *et al*. [91] Wang., *et al*. [92] Wang., *et al*. [92] Wang., *et al*. [92] Wang., *et al*. [92] Jin., *et al*. [94] Jin., *et al*. [94] Jin., *et al*. [94]

Table 2: *Molecular effects of polyphenols.*

Polyphenols	Up-regulate	References	Inhibit	References
Stilbenes [Resveratrol]	AMPK PPARα SIRT1 DNMTs LINE-1 SOD Bcl-2 Catalase GSH-PX GSH HO-1 Autophagy SAPK/JNK	Nagai., *et al*. [101] Qin., *et al*. [106] Maugeri., *et al*. [107]; Zhang., *et al*. [108] Maugeri., *et al*. [107] Maugeri., *et al*. [107] Yang., *et al*. [110]; Hua., *et al*. [111] Yang., *et al*. [110] Hua., *et al*. [111] Hua., *et al*. [111] Hua., *et al*. [111] Neal., *et al*. [112] Koskela., *et al*. [114]; Josifovska., *et al*. [115] Balaiya *et al* [116]	ROS MAPKs ICAM-1 MCP-1 NLRP3 Caspase-1 IL-1β IL-8 ROS COX-2 A2E MDA VEGF-R2 CXCL11 CXCL9 CCL2 CCL5 NF-κB VEGF	King., *et al*. [97] Chan., *et al*. [19], King., *et al*. [97], Balaiya *et al* [116] Nagai., *et al*. [101] Nagai., *et al*. [101] Bhattarai., *et al*. [102] Bhattarai., *et al*. [102] Bhattarai., *et al*. [102] Bhattarai., *et al*. [102] Nashine., *et al*. [104] Chan., *et al*. [19] Kang., *et al*. [105] Yang., *et al*. [110] Courtaut., *et al*. [117] Kutty., *et al*. [118] Kutty., *et al*. [118] Kutty., *et al*. [118] Kutty., *et al*. [118] Nagai., *et al*. [101]; Kutty., *et al*. [118] Dugas., *et al*. [99]; Bhatt., *et al*. [100]; Nagai., *et al*. [101]

Curcumin	Nrf2 PI3/Akt HO-1 TRX1 Bcl-2 SOD GSH GSH-PX NQO1	Mandal., *et al*. [127]; Li., *et al*. [131] Li., *et al*. [131] Mandal., *et al*. [127]; Chang., *et al*. [132]; Muangnoi., *et al*. [133] Mandal., *et al*. [127] Zhu., *et al*. [128]; Muangnoi., *et al*. [133] Zhu., *et al*. [128]; Chang., *et al*. [132] Zhu., *et al*. [128]; 1 Li., *et al*. [131] Chang., *et al*. [132] Muangnoi., *et al*. [133]	NF-κB VEGF ROS Bax Caspase-3 MDA A2E MAPKs	Mandal., *et al*. [127] Alshamrani., *et al*. [130]; Chang., *et al*. [132]; Allegrini., *et al*. [134] Zhu., *et al*. [128]; Alshamrani., *et al*. [130]; Chang., *et al*. [132]; Muangnoi., *et al*. [133] Zhu., *et al*. [128]; Muangnoi., *et al*. [133] Zhu., *et al*. [128] Zhu., *et al*. [128] Park., *et al*. [129] Park., *et al*. [129]; Muangnoi., *et al*. [133]

Table 3: *Molecular effects of polyphenols.*

Conflicts of Interest

None.

Criteria for Inclusion in the Authors/Contributors List

Active participation in the research, article drafting and revision.

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