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A Renewed Concept on Diabetic Retinopathy: Polyphenols as a Choice of Solution

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Abstract: Diabetic retinopathy (DR) is the widespread microvascular consequence of diabetes mellitus and the most common effect of blindness in people with diabetes. Existing drugs are only effective in advanced stages of DR, and long-term efficacy and safety results for these treatments have yet to be clarified in multiple clinical trials. Furthermore, a more trustworthy and effective medication that may be deemed more advantageous in managing DR is unavoidable. Polyphenols, which are plant-derived chemical compounds, may be helpful in the initial stages of DR treatment. Compounds rich in polyphenols have been shown to slow the progression of long-term consequences of diabetes, for example, heart disease, nerve damage, kidney damage, and retinopathy. Polyphenols could be used instead of traditional treatments to halt the disease's progression. It has been proposed that *in vitro* investigations on the effects of polyphenols on ocular vision physiology and antioxidant protection have a substantial bearing on this assertion. Among the benefits of polyphenols are scavenging the free radicals, lowering the production of advanced glycation end products, inhibiting aldose reductase, anti-inflammatory activity, and affecting ocular blood flow. The present review discussed the significance of polyphenols in preclinical and clinical research of DR-affected cellular and molecular pathways.

Keywords: polyphenols; diabetes retinopathy; oxidative stress; reactive oxygen species; a clinical study.

1. Introduction

Diabetes mellitus (DM) is a metabolic condition triggered by an inability to produce or use insulin. Diabetes has significant socioeconomic effects since it affects many populations [1]. The diabetes epidemic severely influences individuals' health and financially impacts

society and healthcare. Cardiovascular system complications, such as diabetic retinopathy (DR), diabetic neuropathy, and diabetic nephropathy, are the most widespread reasons for death among people with diabetes. DR is an essential microvascular difficulty of diabetes, the primary trigger of vision loss and blindness worldwide, with a neurodegenerative component. As the disease becomes increasingly frequent, the number of people with diabetes-related kidney disease (DRKD) is anticipated to rise to 191 million by 2030 [2].

The retina's microvasculature has been destroyed, and penetration has increased due to DR, leading to blindness in the long run. According to studies, animal models with thinner retinas appear to have fewer retinal ganglion cells. Furthermore, apoptosis occurs more quickly in those retinas as dead cells increase, even before histopathological indications appear [3].

Many components and metabolites affect the diabetic animal's retinas, causing retinal cell destruction and influencing disease development. Oxidative stress (OS), which cooperates with many signaling routes, is one of the most critical components in the complicated process of diabetes [4]. DR has been linked to various metabolic processes that are difficult to comprehend, including the heightened development of advanced glycation end products (AGE), protein kinase C activation (PKC), and stimulation of the polyol and hexosamine pathways [5]. The diabetes retina's dysregulation of different metabolites affects a diversity of intermediaries, including cytokines, chemokines, growth factors, neurotrophic factors, and adhesion molecules. An expansion in OS in retinal cells causes DR [6].

Nature offers diverse therapeutically beneficial compounds with fewer side effects and lower costs. These naturally produced compounds, such as alkaloids, tannins, polyphenols, terpenoids, flavonoids, and steroids, have a variety of pharmacological activities that target many metabolic pathways [7]. These spontaneously produced molecules' improved intercellular medication distribution is critical in creating sound therapeutic effects [8,9]. The capacity of plant-derived chemical agent polyphenols to increase the intercellular drug transport mechanism is essential to establishing favorable treatment outcomes for DR [10,11]. This review highlighted the importance of polyphenols in treating various ailments and their potential relevance in developing novel therapeutics for diabetes-related retinal damage.

2. Risk Factors and Epidemiology

Compared to their research in 2010 [12], the Visual Loss Expert Group's most recent report in 2015 found that DR has slipped from 5th to 6th position as the highly prevalent trigger of avoidable vision impairment globally [13]. Even though all reasons for blindness and vision impairment have decreased, DR was the only one that remained blind, an eye ailment that has been more common globally since 1990. DR mild-to-moderate vision impairment boosted by 7.7%, while DR moderate-to-severe vision impairment increased by 28.6%. This red flag in 2015 indicated that the existing screening system needed to be beefed up. Before the commencement of the illness, increase research programs directed at novel molecular targets and management strategies targets [13,14].

The worldwide predominance of DR was expected to be 34.6% for all types of DR in 2010, 6.81 % for diabetic macular edema (DME), and 6.96 % for proliferative diabetic retinopathy (PDR), and 10.2% for vision-threatening diabetic retinopathy (VDR) in 2010. Retinopathy includes conditions like PDR and DME. This equates to around a third of the total population. Because of DR, one-tenth of diabetics will require active therapy. The risk of acquiring a DR was 2.7 times superior in thin type 1 diabetes (T1DM) than in type 2 diabetes (T2DM). T2DM is a kind of diabetes that develops after at least 20 years [15]. The latest nine-

year prospective research study comprising T1 and T2 patients reported a 15.16 to 2.19% yearly incidence in T1DM, compared to 8.37 to 2.19% in T2DM. Low-density lipoprotein (LDL) cholesterol and arterial hypertension are all under control in DM duration and glycaemic management. In both T1DM and T2DM patients, high creatinine levels were revealed to be substantial risk factors for DR progress. The T1DM sample had a more significant predominance and occurrence of DR at the end of the trial. This study found a link between having diabetes for more extended and having lower basal and measured glucose levels [16].

There is proof that oily fish, dietary fiber, and Mediterranean help guard against DR in nutritional practices. Conversely, higher-calorie consumption has been related to a higher risk of DR. Furthermore, antioxidants, particularly vitamins C, E, and carotenoids, act as defensive agents, according to a recent study on antioxidants in typical diets [17].

3. Pathophysiology of Diabetic Retinopathy

DR must be regarded as multifactorial since it develops directly from persistent hyperglycemia, despite being impacted by the risk factors previously discussed [18–20]. From a metabolic aspect, OS was discovered to play a vital role in the growth of DR, acting as a relationship between many variables. Glucose-mediated biochemical activities, an excess of glucose, cause the mitochondria to become activated. The polyol pathway, the manufacture of AGEs, and their activation improve PKC and increase the hexosamine pathway. These variables boost the reactive oxygen species (ROS) production [21–23]. These molecules are regularly generated for regular cell activity. The body's antioxidant capabilities assist in neutralizing the effects (Figure 1).

Furthermore, the accumulation of ROS leads to changes in mitochondrial DNA structure, which leads to changes in gene expression. ROS accumulation is exacerbated in mitochondrial malfunction [23,24] because OS has a long-term influence on diabetes. Even when correct glycaemic management is established, this phenomenon, known as metabolic memory, has been hypothesized to cause disease development [24]. Glycaemic-induced OS is exacerbated by arteriosclerosis, which worsens molecular damage [25]. Cellular dysfunction and apoptosis are caused by hyperglycemia-induced metabolic alterations and ROS increase [26].

3.1. Inflammation.

Microglial activation is a preliminary result of DR growth and can produce inflammatory mediators [27,28]. Pro-inflammatory cytokines are found at higher human concentrations (interleukins IL-1β, IL-6, IL-8, and TNF-α). Vitreous samples have also been correlated with the seriousness of DR [29-31]. In response to inflammatory stimuli, endothelial cells enhance the manifestation of intracellular and extracellular proteins. Leukocyte adherence is facilitated by E-selectin and vascular adhesion molecules (ICAM-1 and VCAM-1). The formation of leukostasis, or the creation of white blood cells, is linked to linkage to endothelial cell walls—a critical factor in the progression of posterior microvascular destruction [32,33]. In diabetes blood samples, higher levels of the components mentioned above were found, and blocking ICAM-1 in diabetic retinal endothelial cells decreased cell death in cultured human retinal endothelial cells [34]. Surprisingly, administering an antioxidant agent reduced cellular loss while lowering the ICAM-1 level in those retinal cells [34].

3.2. Neurodegeneration.

Programmed cell death appears to influence neurons before vascular cells in neurodegeneration. Before the onset of DR clinical symptoms and microvascular changes, electroretinogram (ERG) tests have suggested remaining neuronal damage. Furthermore, diabetic animal models and human participants reduced the ganglion cell inner layer [35,36]. ERG tests were conducted on induced-diabetes mice pre and post-antioxidant treatment to study the defensive impact of lutein on visual purpose and histological neuronal variations related to OS about neurodegeneration [37].

3.3. Pericytes layer.

A basement membrane, an external pericytes layer, and an interior endothelial cells layer contribute to micro-vasculopathy in retinal capillaries. Pericyte loss occurs in hyperglycemic conditions [38], leading to localized microvascular dilatation and microaneurysms. Debris deposition and endothelial cell failure show the disturbing blood-retinal barrier (BRB), enhancing vascular absorptivity, exudation, and hemorrhages [39]. Leukostasis, which results from an inflammatory reaction, damages endothelial cells and leads to microvascular occlusions [40]. Following hypoxia, the transcription factor hypoxia-inducible factor 1 (HIF-1) is activated, which enhances the release of vascular endothelial growth factors (VEGFs) and leads to the creation of neovessels [41].

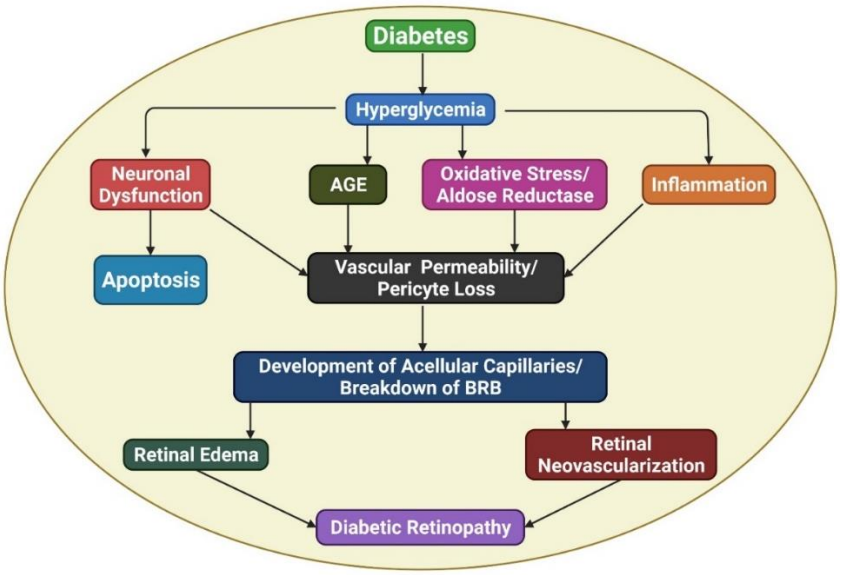

Figure 1. Diabetic retinopathy Growth and progress. A.G.E., advanced glycation end products; BRB, blood-retinal barrier.

4. Polyphenols and Diabetic Retinopathy

A group known as polyphenols or polyphenolics is naturally occurring and extensively dispersed in the kingdom of plants [42]. These compounds are distinguished by aromatic rings attached to phenol structural units. Regarding physical, biological, and metabolic qualities and functions, these secondary metabolites of plants are primarily defined by their phenol structural units. Polyphenols are split into two primary categories established on their molecular structure: flavonoids and non-flavonoids (Figure 2). Stilbenes, phenolic acids, lignans, and other polyphenols are subclassified as non-flavonoids [43]. Flavonoids are polyphenolic

molecules in vegetables and fruit, accounting for approximately 60% of total polyphenols [44]. Flavonoids can be divided into six subtypes: flavanol, flavones, flavanones, isoflavonols, flavonols, and anthocyanin-containing flavonols [45].

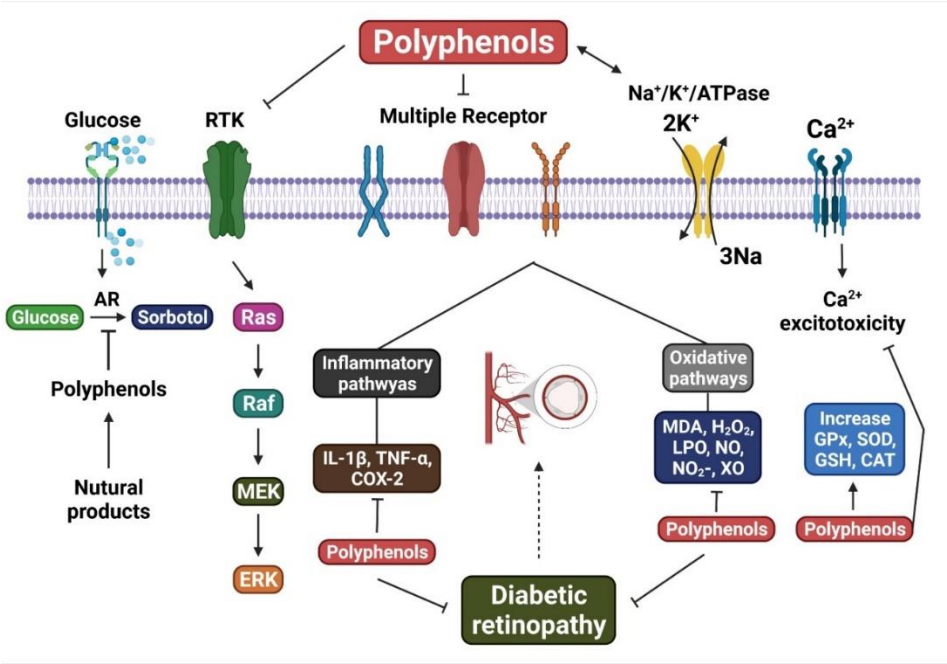

Figure 2. Mechanistic role of polyphenols against diabetic retinopathy. TNF-α, tumor necrosis factor alpha; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; LPO, lactoperoxide; NO, nitric oxide; XO, xanthine oxidase; MDA, malondialdehyde; CAT, catalase; SOD, superoxide dismutase; GSH, glutathione; GPx, glutathione peroxidase.

4.1. Resveratrol.

Resveratrol (RSV)) is abundant in blueberries, raspberries, mulberries, red wine, and grape skin [46]. Anti-angiogenic, antioxidant characteristics, antiproliferative, antiplatelet, endothelial, anti-inflammatory, and neurogenic capabilities are all found in RSV [47]. When administered orally, RSV is absorbed 75%, primarily by trans epithelial diffusion, but bioavailability is less than 1%. This is because glucuronidated chemicals are engaged and sulfated to easily remove essential metabolites in the colon and liver. On the other hand, bioavailability varies substantially between people due to considerations including age and gender [47–49]. Because RSV is a hydrophobic molecule, it is captivated by intestinal epithelial cells, hepatocytes, and breast carcinoma cell lines [47]. Resveratrol therapy was revealed to increase diminished glutathione (GSH) levels in erythrocytes and the ocular degree in rats, where GSH serves as an antioxidant [50,51]. RSV restrains the action of an enzyme associated with neovascularization, endothelial nitric oxide synthase, and inflammatory processes in rats' eyes [52,53]. In diabetes, RSV therapy reduces the number of vascular leaks, pericyte loss, and VEGF levels. According to Luna *et al*., RSV reduced ROS production, which prevented the development of pro-inflammatory markers such as IL-1β, IL-6, and IL-8 [54].

4.2. Curcumin.

Curcumin is a crystalline orange-yellow combination that is one of *Curcuma* spp. Main's components [55]. The WHO recommends daily consumption of 0-3 mg/kg as a dietary ingredient [56]. Recently, curcumin has been beneficial in treating DR. Curcumin performs as an antioxidant by diminishing free radicals [57]. Curcumin boosts the mRNA appearance of

antioxidant enzymes like SOD and catalase, decreasing oxidative and synchronizing nitrosative DNA destruction [58]. Curcumin stimulates a mitochondrial pathway by altering the respiratory activity of mitochondrial complexes I, II, III, and V while simultaneously activating erythroid 2-related factor 2 (Nrf2) [59]. Curcumin can enhance antioxidant capability and hypoglycemic and prophylactic anti-inflammatory action in diabetic rats' retinas by cutting pro-inflammatory cytokines levels like IL-1β, TNF-α, and VEGF [60,61], as well as 5-hydroxyeicosatetraenoic acid and a dual inhibitor of arachidonic acid [62]. Curcumin is an anti-angiogenic agent that lowers stromal cell-derived factor 1 alpha and inhibits retinal human endothelial cells [63].

4.3. Quercetin.

Quercetin protects the retinas of diabetic patients from a range of injuries [64,65]. High glucose-stimulated irritation and programmed cell death generated IL-6, monocyte chemoattractant protein-1 (MCP-1), and ROS, which were decreased by quercetin. MiR-29b may be a good target for DR control since its anti-angiogenic impacts on diabetic animals' retinas by reducing RME production, relocation, and angiogenesis. Additionally, ARPE-19-treated cells have increased miR-29b expression, and lower miR-29b expression has been associated with a diminished quercetin protective effect in patients [66]. Therefore, the PTEN/Akt pathway stimulus and the inhabitation of the nuclear factor kappa B (NF-κB) path are primarily due to miR-29b expression [67]. *In vivo*, quercetin reduced caspase-3 and NF-κB expression, indicating antiapoptotic effects [68]. This flavonol is also responsible for inactivating neovascularization-related proteins like VEGF and MMP-99. Quercetin decreased TNF-α and IL-1β levels while increasing antioxidant enzymes (CAT, SOD, and GSH).

Expression of the AQP4 and GFAP were also inhibited by quercetin [68,69]. Another investigation discovered that quercetin has anti-diabetic effects in STZ-induced diabetic rats. An intraperitoneal quercetin dose significantly reduced IL-18, IL-1β, TNF-α, IL-6, and NLRP3 inflammasome over-activation at a 150 mg/kg dose for 16 days ganglion cells and thickness of the retinal cell layer were improved [65].

4.4. Catechins, epicatechin, epigallocatechin and epigallocatechingallate.

Catechins are derived from natural sources (grapes, cocoa) and red wine, although green tea and chocolates have the highest concentrations. Catechin and epicatechin are key flavanols found, whereas gallocatechin, fruits, epigallocatechin, and epigallocatechin gallate are primarily found in leguminous plant seeds [70]. The aggregation of advanced glycation end products (AGEs) plays a direct part in the turning on and improvement of DR [71]. Kim and colleagues studied the probable outcomes of AGE-injected rats in an *in vivo* and *in vitro* study. Combining (-)-epicatechin and glycated human serum albumin detached from diabetic patients increased AGE breakdown. The treatment of (-)-epicatechin in exogenously AGE-injected rats reduced retinal vascular apoptosis and the retina's AGE burden. As a result, (-)-epicatechin could be a promising treatment option for DN [72]. Skopinski *et al*. found that flavanols isolated from plants, including epigallocatechin (EGC) and epigallocatechin gallate (EGCG), inhibited the angiogenic actions in rats considered [73]. Green tea (*Camellia sinensis*) is a sustainable supplier of antioxidants, primarily due to its high flavonoid content, including EGCG [74]. Green tea has been shown to have therapeutic consequences in contrast to glutamate toxicity in diabetic rat retinas. Green tea extracts were found to reduce retinal

problems in diabetic rats; according to Silva *et al*., Green tea reduced elevated glial fibrillary acidic protein (GFAP), glutamine synthetase, and oxidative retinal indicators. In diabetic rats treated with tea extract, N-methyl-D-aspartate R1 (NMDAr1), glutamate aspartate transporter (GLAST-1), and obstructing were likewise lowered. These results suggest that EGCG could be an effective treatment for DR. Due to high glucose levels, Müller cells produced too much glutamine synthetase and ROS but insufficient glutamate transporter, GSH, or glutamate receptor. Green tea treatment effectively reversed all changes mentioned above in diabetic rats' retinal cells [75].

Zhang *et al*. examined the effect of EGCG on the HREC line. The cell viability, cell cycle, and mortality were studied using the MTT assay and flow cytometry. According to the findings, medication of HRECs with EGCG dramatically reduced programmed cell death. EGCG also suppressed VEGF expression and lowered the expression of ERK1/2 and MAPK [76]. In the last stages of DR, metalloproteinase-9 (MMP-9) aids vascular penetrability and neovascularization. The effective primary constituent of green tea extract, EGCG, inhibited TNF-α and MMP-9 production in human retinal pigment epithelial cells 12-O-tetradecanoylphorbol-13-acetate (TPA) (HRPECs). In ARPE-19 cells, EGCG consumption inhibited apoptosis by dropping ROS levels and decreasing mRNA expression of VEGF, MMP-9, and VEGF Receptor-2. Moreover, in VEGF-treated HRPECs, EGCG administration dramatically inhibits proliferation, tube formation, and vascular permeability. EGCG reduced vascular leakage and permeability in animal studies [77]. In another study, EGCG improved autophagy in Müller cells by enabling autophagosome formation, boosting lysosomal acidity, and boosting autophagic flux. Furthermore, it increased cell proliferation, protected cells from apoptosis, and decreased retinal destruction produced by high glucose levels [78].

4.5. Rutin

Rutin reduces apoptosis in the diabetic retina by decreasing caspase-3 and raising neurotrophic elements (BDNF and nerve growth factor (NGF)) as well as Bcl-2 levels [79]. Furthermore, rutin therapy reduced TNF-α, aldose reductase protein, and VEGF expressions, restoring fluorescein vascular seepage. It also can boost overall antioxidant activity in the retina [80].

4.6. Galangin

Galangin flavonol reduced blood-retina barrier (BRB) breakdown by reducing inflammation caused by microglia and so repaired BRB malfunction caused by TNF-α [81] via increasing the Nrf2 pathway. Galangin therapy boosted strong intersection enzyme representation and diminished BRB destruction in ARPE-19 cells and HRECs exposed to TNF-α. Galangin also mimicked the initiation of Nrf2 and the decrease of ROS construction, resulting in the alteration of many antioxidant genes [81].

4.7. Kaempferol

Protein, mRNA for a placenta growth factor (PGF), and VEGF were raised in HRECs under hyperglycemic conditions. To reduce angiogenesis, kaempferol treatment reduced the expansion of angiogenic factors. Anti-angiogenic effects of kaempferol are further demonstrated by inhibiting phosphorylation processes of specific kinases (Akt1, Erk1/2, and Src) beside PI3K manifestation induced by hyperglycemia [82]. Digestive enzymes, α-

glucosidase and β-amylase, are responsible for converting hydrolyzed carbohydrates into glucose that can be absorbed. Kaempferol slowed down these enzymes' activity leading to a lower and more stable blood sugar spike after a meal. This is a significant way to manage T2DM [83].

In addition, kaempferol was tested to protect RGCs from high-glucose-induced damage. At a concentration of 0, 20, 40, 60, 80, or 100 mol/L, RGC cells were exposed to kaempferol and increased glucose (55 mmol/L) for 48 h. After testing, it was discovered that treatment with kaempferol dramatically reduced ROS levels, caspase-3 activity, lactate dehydrogenase leakage, and cell death. The extracellular signal-regulated kinase (ERK) phosphorylation and expression of vasohibin-1 (VASH1) were also increased by kaempferol, which inhibited ERK phosphorylation [84] (Table 1).

Table 1. Preclinical investigations of polyphenols in the protection of diabetic retinopathy.

Bioactive compound	Sources	Dose/Concentration	Study model	Outcomes	Refs
Resveratrol	Grapes, berries and peanuts	5 mg/kg/day; Four months	STZ-nicotinamide-stimulated diabetic retinopathy	Decreased superoxide dismutase function and oxidative stress	[85]
Resveratrol	Red wine and grape skin	5, 50, 100, or 200 mg/kg; 5 days	Male C57/B6 mice	Lowered ICAM-1 and MCP-1 protein levels in the retina	[86]
Resveratrol	Grapes, berries and peanuts	5, 10, or 50 µg/kg/day; 12 weeks	STZ-mediated diabetic rats	Retinal vascular penetrability and inflammatory arbitrators such as Ox-LDL, LDL, MCP-1, A.G.E.s, IL-1β, IL-6, IFNγ, and VEGF were reduced.	[87]
Resveratrol	Red wine and grape skin	20 mg/kg; 4 weeks	STZ-intervened diabetic rats	By suppressing retinal CAMKII activity, the NF-κB was downregulated.	[88]
Curcumin	*Curcuma longa*	100 and 200 mg/kg; 16 weeks	Diabetic rat model	Diabetes-stimulated retinal ultrastructure alterations include retinal ganglion cell death, retinal shrinkage, and photoreceptor cell membrane disruption.	[89]
Curcumin	*Curcuma longa*	80 mg/kg; daily	STZ-mediated diabetic rats	GSH levels were not depleted, and oxidative stress was reduced.	[90]
Curcumin	*Curcuma longa*	1 g/kg; 16 weeks	STZ-mediated diabetic rats	VEGF, TNF-α expression, and GSH, CAT, and SOD levels were reduced.	[61]
Quercetin	Fruits and vegetables	20, 40, 80 µmol/L; daily	High-glucose exposed HRECs	Diminished angiogenesis and apoptosis; lowered caspase-1, IL-18, Beclin-1, and NLRP3 expression.	[91]
Quercetin	Fruits and vegetables	150 mg/kg; 16 days	STZ-stimulated diabetic rats	TNF-α, IL-6, IL-18, and IL-1β expressions were decreased, and the	[65]

Bioactive compound	Sources	Dose/Concentration	Study model	Outcomes	Refs
				NLRP3 inflammasome was overactivated.	
Quercetin	Fruits and vegetables	10, 20, 30, 40, and 50 μM; 1 day	ARPE-19 cells treated with high glucose	Reduced expression of Bax, p53, and cleaved caspase-3; reduced apoptosis, IL-6, MCP-1, and ROS generation	[92]
Catechin	*Camellia sinensis*	50, 100, and 200 mg/kg; 8 weeks	STZ-mediated diabetic rats	Suppressed the NF-κB pathway, lowering IL-1β, IL-6, and TNF-α levels while increasing HSP27 levels.	[93]
(-)-epicatechin	Cocoa and green tea	50 mg and 100 mg/kg; 2 weeks	AGE-treated rats	Increased AGE splitting action and reduced AGE load; enhanced retinal vascular programmed cell death	[94]
EGCG	*Camellia sinensis*	0, 10, 20, 30, 50 μM; 24 hours	Glucose-exposed retinal Müller cells	Increased cell growth and apoptosis; reduced retinal degeneration	[78]
EGCG	*Camellia sinensis*	5.7 g/kg; 12 weeks	STZ-mediated diabetic rats	BRB breakdown is reduced; the occludin, GLAST, and NMDAr1 subunits are attenuated; electroretinography recordings are improved; reduced amounts of glutamine synthetase and GFAP	[75]
EGCG	*Convallaria majalis*	2, 20, and 200 μg/ml; every day	Balb/c mice	Suppression of angiogenic functions	[73]
EGCG	*Camellia sinensis*	20 and 40 mM; 24 hours	High glucose-treated HRPECs	Decreased apoptosis; decreased ERK1/2 and MAPK expression; suppressed VEGF expression.	[73]
EGCG	*Camellia sinensis*	200 mg/kg EGCG; 4 days	VEGF-treated Sprague-Dawley and balb/c mice	BRB breakdown was reduced, and vascular leakage was also reduced.	[76]
Rutin	Onions, tea, apples, and red wine	100 mg/kg; 5 weeks	STZ-facilitated diabetic rats	Bcl-2, G.S.H., NGF, BDNF, and blood insulin levels were elevated, while TBARs, caspase-3, and blood sugar levels were reduced.	[77]
Rutin	Onions, tea, apples, and red wine	50 mg/kg; 24 weeks	STZ-facilitated diabetic rats	TNF-α, VEGF, and aldose reductase levels decreased, fluorescein vascular seepage lowered, and antioxidant potential increased.	[79]
Galangin	*Alpinia officinarum*	20 and 50 μM; 6 hours	Microglial BV2 cells handled with D-glucose	Reduced NF-κB, TNF-α, and Egr1 protein levels; reduced ROS generation, phosphorylate n of ERK1/2, microglia cells, and BRB degradation.	[80]

Bioactive compound	Sources	Dose/Concentration	Study model	Outcomes	Refs
Kaempferol	*Kaempferia galanga*	0, 20, 40, 60, 80, or 100 μmol/L; 48 hours	High-glucose stimulated injury in RGC cells	Reduced R.O.S. levels, caspase-3 activity, lactate dehydrogenase permeability, and death; suppressed ERK phosphorylation while increasing ERK phosphorylation and production of vasohibin-1 (VASH1)	[95]
Kaempferol	Tea, grapefruit, broccoli	5 and 25 μM; 1 day	HRECs handled with high glucose	Lowered PI3K expression, PGF mRNA, and VEGF levels; Src, ERK1/2, and Akt1 initiation decreased.	[84]
Puerarin	Pueraria plants	250 and 500 mg/kg; 4 weeks	STZ-facilitated diabetic rats	MDA and STAT3 levels have decreased, while SOD activity has enhanced.	[96]
Puerarin	Pueraria plants	80 mg/kg; 4 weeks	STZ-mediated diabetic rats	Inhibited AGE-modified protein levels	[97]
Puerarin	*Pueraria lobata*	1, 5, and 10 μM; 1 hour	Bovine retinal pericytes exposed to AGE-BSA	Lowered ROS generation and NADPH oxidase function; lessened NF-kB stimulation and phosphorylation of p47phox and Rac1	[98]
Puerarin	*Radix puerariae*	10, 25, and 50 μM; 24 hours	TR-iBRB2 cells treated with IL-1β	Expression of ICAM-1, VCAM-1, and Bcl-2 is reduced; Cell death, leukostasis, and mitochondrial dysfunction are reduced, and NO and SOD synthesis are increased.	
Puerarin	Pueraria plants	125, 250, and 500 mg/kg; 4 weeks	STZ-facilitated diabetic rats	Reduced NF-κB p65 activation and apoptotic in retinal cells	[99]
Naringenin	Citrus fruits	50 mg/kg; 5 weeks	STZ-treated diabetic rats	G.S.H., Bcl-2, TrkB, BDNF, and synaptophysin levels were raised; Bax, TBARs, and caspase-3 levels were significantly lower.	[100]
Eriodictyol	*Eriodictyon californicum*	0.1, 1, and 10 mg/kg; 10 days	STZ-handled with diabetic rats	Reduced plasma lipid peroxidation; reduced ICAM-1, eNOS, TNF-α, and VGEF expression; inhibited BRB degradation.	[101]
Eriodictyol	*Eriodictyon californicum*	5, 10, and 20 μM, one day	RGC-5 cell line treated with high glucose	Reduced IL-8 and TNF-α; synthesis of ROS was reduced; decreased cell mortality; enhanced Nrf2 nuclear translocation C.A.T., GPx, and SOD activities have all	[102]

Bioactive compound	Sources	Dose/Concentration	Study model	Outcomes	Refs
				improved; increased expression of heme-oxygenase-1 and cell viability.	
Diosmin	Dehydrogenation of hesperidin	0.1, 1, and 10 μg/mL	ARPE-19 cells treated with high glucose	Phosphorylation of JNK and p38 is reduced; Caspase-3, R.O.S., and cytochrome c release were all inhibited; Bcl-2/Bax and cell growth have enhanced.	[103]
Chrysin	Honey, propolis, honeycomb, and passion flowers	1, 10, and 20 μM; 3 days	RPE cells treated with high glucose	Lowered ER stress; lower levels of IGF-1, VEGF, and PEDF; lessened AGE release and RAGE production	[104]
Chrysin	Honey, propolis, honeycomb, and passion flowers	10 mg/kg; 10 weeks	db/db mice	The development of RAGE and the release of AGE were both inhibited.	[105]

4.8. Anthocyanins.

Anthocyanins are flavonoids found in berries with anti-inflammatory properties [106,107]. Anthocyanins lower several illnesses, including cardiovascular disease, neurological disease, and cancer [108]. Berry anthocyanins also improve brain neuronal and cognitive function. Anthocyanins can prevent OS and its products and the production of pro-inflammatory molecules [109,110]. Anthocyanins have been demonstrated to treat ocular diseases like DR [109] effectively. According to Song *et al*. [111], anthocyanins protect diabetic optic cells against oxidative damage and inflammation.

4.9. Puerarin.

Teng and colleagues investigated Puerarin's antioxidant and antiapoptotic activities in diabetic retinopathy rats. The STZ. group, the STZ. + Puerarin group and the control group were among the three groups in the study. Reverse transcription-polymerase chain reaction (RT-PCR), retinal histopathology, and electron microscopy were used to investigate the consequences of Puerarin on VEGF and HIF-1 gene expression. The morphological modification in both the medial and lateral nuclear layers was downregulated by Puerarin, which decreased the DR produced by STZ. The VEGF and hypoxia-inducible factor (HIF-1) in DR rats were also influenced by puerarin therapy. According to another study, when linked to the non-treated group, puerarin therapy thickened the outer nuclear layer (ONL) and increased the b-wave amplitude. However, in diabetic rats' retinas, puerarin isoflavones increased SOD activity while decreasing AGE buildup, VEGF levels, and STAT3 activity [112].

Puerarin therapy prevented the manifestation of various genes and proteins linked to cell death in retinal cells, including complement 3, nitro-tyrosine (NT), inducible nitric oxide synthase (iNOS), mRNA, and Fas/Fasl [113]. In rat retinal pericytes, Puerarin similarly reduced BSA-induced apoptosis [98]. According to the findings by Zhu *et al*., Puerarin's therapeutic benefits in RCEs against IL-1β-induced cell dysfunction were also examined. Puerarin suppressed both apoptosis and leukostasis [99]. Cai *et al*. studied the impacts of

Puerarin on diabetic rats. A control group, a low-dose puerarin group (250 mg/kg), and a high-dose puerarin group (500 mg/kg) of rats were randomly assigned. Following a 4-week treatment, malondialdehyde (MDA) and STAT3 levels declined considerably, while SOD activity improved. Puerarin also restored the amplitude of the b-wave in electroretinography [97]. Puerarin's effects on AGE-modified proteins in diabetic rats' blood and retinal tissues were studied by Liu *et al*. Puerarin treatment decreased the amount of AGE-modified proteins while preventing pathogenic changes [114].

Puerarin lowered MDA and ROS levels in NMDA-induced retinal cells, downregulated nNOS expression, and boosted SOD and NO generation. Caspase-3 activity and Bax expression were decreased, and p38 and JNK inhibition were blocked [115]. The buildup of intracellular sugar alcohols has been shown to boost aldose reductase activity in retinopathy patients. 3,6,7,4′,5′-pentamethoxy-5,3′-dihydroxyflavone isoflavones isolated from Caesalpiniapulcherrima hampered aldose reductase, prolonging the start of DR. It also reduced the production of TBARs and proteins while boosting the action of antioxidant enzymes such Gpx, C.A.T., and SOD [116].

4.10. Naringenin.

Grapefruit, oranges, and lemons contain the major flavanone components: naringenin, eridicytol, and hesperetin. Furthermore, the chemical structures of such molecules are particularly reactive since they are subjected to o-methylation, hydroxylation, and glycosylation [117]. By reducing GSH and thiobarbituric acid reactive chemicals concentrations in STZ-stimulated diabetic mice, Al-Dosari *et al*. discovered that naringenin had antioxidant, antiapoptotic, and neuroprotective properties [101]. Another study looked at the consequences of naringenin on sodium iodate (NaIO3)-induced rat retinopathy and ARPE-19 cells treated with $NaIO_3$. Carbonyl protein, ROS, and lactic dehydrogenase (LDH) were all discovered. The researchers found that naringenin therapy improved retinal function while lowering Sirtuin 1 protein levels (SIRT1). Carbonyl protein, ROS, and LDH were reduced [118].

4.11. Eriodictyol.

Because it modulates the Nrf2/HO-1 pathway, Eriodictyol possesses anti-inflammatory and antiapoptotic effects. Eriodictyol therapy reduced retinal inflammation in diabetic rats by lowering ICAM-1, eNOS, VEGF, and TNF-α levels. By lowering these mediators' activity, eriodictyol could restore BRB degradation. Eriodictyol [119] reduced ROS production and prevented plasma lipid peroxidation. *In vitro*, eriodictyol has lower ROS concentrations and OS while increasing S.O.D., GPx activity, and C.A.T. Eriodictyol also improved cell survival, nuclear translocation of Nrf2, and the synthesis of heme-oxygenase-1, all of which are significant OS regulators [103].

4.12. Diosmin.

A flavone glycoside in sour fruits, diosmin(30,5,7-trihydroxy-40-methoxy flavone-7-rhamnoglucoside), can protect against cardiovascular disease [120]. Diosmin, the primary ingredient in Daflon nutraceuticals, can treat symptoms of venous insufficiency. This medication can also be used to treat hemorrhoidal crises [121]. Diosmin effectively protected BRB in an ischemic/reperfusion injury paradigm by lowering VEGF representation and

decreasing edema [122]. As a result, diosmin reversed the I/R-induced alterations in retinal ganglion cell count and electroretinogram, which were likewise reversed by diosmin. In the retina, diosmin administration decreased MDA and increased GSH-Px, C.A.T., and SOD activity [123]. Furthermore, diosmin treatment of ARPE-19 cells increased cell survival by lowering apoptosis, reducing ROS production, and increasing SOD and GSH-Px activity [104].

4.13. Chrysin.

Chrysin protects against visual cycle impairment initiated by hyperglycemia. Chysin inhibited hyperglycemia-induced neovascularization in retinal pigment epithelium (RPE) cells by lowering IGF-1 and VEGF levels while increasing pigment epithelium-derived factor (PEDF) levels [105]. After Chrysin administration, the external nuclear layer thickness of the db/db mice retina improved, as did the stories of visual cycle-related enzymes (RDH5 and lecithin retinol acyltransferase (LRAT)) [105]. AGE and RAGE induction generation was diminished in a high-glucose RPE cell line treated with chrysin, but RPE65, RDH5, PEDF, and LRAT were elevated. Chrysin also inhibited endoplasmic reticulum stress sensor proteins (ER stress proteins), and the visual cycle was restored by controlling the AGE/RAGE pathway [105].

5. Clinical Trials

Phytochemicals have been shown to protect against DR in various non-clinical investigations. Still, just a few clinical studies have looked into how phytochemicals help protect diabetes and DR. A clinical examination was conducted on 564 patients out of 10,054 to determine the likelihood of having diabetes. The flavonoids myricetin and quercetin were reported to reduce diabetes mellitus [126] dramatically. In addition, a meta-analysis of RCTs with 1584 participants looked at the consequences of catechins, including or not including caffeine, on diabetes biomarkers. Green tea catechins reduced fast blood glucose concentrations considerably however did not affect glycated hemoglobin (HbA1c) or fasting blood insulin levels [124]. The efficacy of oral Melilotus and Centella Asiatica flavonoids in treating diabetic cystoid macular edema was studied in another RCT comprising 70 T2DM patients. According to the study, flavonoids preserved retinal sensitivity but did not influence HbA1c levels, blood pressure, central retinal thickness, visual acuity, and microalbuminuria [125]. Furthermore, fasting glucose and serum adiponectin were significantly lowered and elevated in 160 diabetic individuals after 12 weeks of treatment with pure anthocyanins [126].

Between 2003 and 2006, Mahoney and colleagues used data from the NHANES to consider the effect of a flavonoid-rich diet on DR and diabetes-related biomarkers in 381 diabetic people. A flavonoid-rich food intake reduced the probability of having DR by 30%. They also reduced glucose, C-reactive protein, and hemoglobin A1C levels [127]. Another one-year study indicated that green tea regularly lowered developing DR by 50% [128]. Pycnogenol® has been found to alter the visual function growth in diabetic patients with DR in a multi-center field study. After six months of treatment with Pycnogenol®, no substantial improvement in patient visibility was reported in 1169 individuals [129,130].

Additionally, oxidative stress and central macular thickness were dramatically reduced after six months of Pycnogenol® treatment [131]. In addition, two months of Pycnogenol® treatment alleviated sensory disturbance in patients with DR in the initial phases [130]. Despite the positive restorative consequences of phytochemicals in diabetes, inconsistent or

contradictory data from clinical trials pose considerable barriers. According to reports, most current investigations focus on T2DM patients and patients at various stages of the condition. As a result, linking phytochemicals to the treatment of diabetes has become increasingly challenging [132] (Table 2).

Table 2. Clinical studies of polyphenols in the management of diabetic retinopathy (DR).

Bioactive compound/ Plant	Dose/Concentration	Duration	Participants	Outcomes	Refs
Chinese green tea	Ingested once a week	One year	100 subjects with DR and 100 diabetic subjects without DR.	DR incidence was reduced by 50% and associated with those not drinking green tea.	[128]
Catechins (Green tea)	-	-	1584 participants	FBG levels are lower; HbA1c and fasting blood insulin levels are unaffected.	[124]
Myricetin and quercetin	-	One year	The possibility of developing diabetes was investigated in 564 of 10,054 participants.	Diminished the possibility of improving T2DM	[133]
Pycnogenol®	60–120 mg, daily	Six months	1169 diabetic subjects having DR.	There was no discernible improvement in the patient's visibility due to the treatment.	[134]
Pycnogenol®	150 mg/day	Two months	46 subjects	Enhancement in appearance and baseline	[130]
Purified anthocyanins	320 mg, daily	12 weeks	160 subjects	Fasting glucose levels were lower, and serum adiponectin levels were higher.	[126]
Melilotus and *Centella Asiatica* flavonoids	Oral administration of 15 mg *C. asiatica*, 300 mg diosminand 160 mg Melilotus, daily	36 months	70 subjects	Blood pressure, visual acuity, and microalbuminuria did not change significantly.	[125]
Flavonoid-rich diet	-	-	381 diabetic patient	Lowered glucose, HbA1C, and C-reactive protein levels by 30%, reducing the progression of DR.	[127]

5. Concluding Remarks and Future Perspectives

Polyphenols can treat DR as a secure and effective substitute for current medications and treatments. Numerous studies in animals and cell cultures have demonstrated that phytochemicals can reduce neurodegeneration and programmed cell death *in vivo* and *in vitro*, improve the oxidative state, lower the construction of pro-inflammatory mediators, and restore retina thickness. Because of the presence of polyphenols, the medicinal impacts of their intervention have been well-established in various clinical studies. According to a few studies, polyphenol supplementation with a balanced diet can help people with diabetes avoid diabetes and associated consequences, such as DR. Another advantage of consuming polyphenols is that it helps prevent DR. Results from preclinical and clinical research indicated that including polyphenols in one's diet can help avoid the development of DR and other vision problems. Instead of treating nutraceuticals as magic bullets that may cure people of their ailments, they should augment a healthy diet.

Additional experimental trials are needed to demonstrate the purpose and relevance of polyphenols in DR. Because the outcomes of some clinical trials have been varied, it is impossible to say whether natural substances have a consistently positive effect on patients. As a result, drawing appropriate conclusions from these investigations takes time and effort. The bioavailability of most polyphenols and other nutraceuticals, such as resveratrol, curcumin, and others, is low, making developing a therapeutic molecule difficult.

Furthermore, the absence of readily available delivery systems for nutraceutical compounds is another possible flaw that must be addressed soon. The retina has only been the subject of many clinical studies due to the nutraceuticals' restrictive delivery paradigm. On the other hand, nanotechnology has substantially improved natural chemical delivery mechanisms through novel technologies. To cure DR more successfully, future research should focus on reducing the barriers limiting nutraceutical medicinal molecules' creation.

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Conflicts of Interest

The authors declare no conflict of interest.

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