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Review

Exploring the Potential of Nutraceuticals in Diabetic Retinopathy: Evidence-Based Mechanisms and Clinical Insights

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Abstract

Diabetic retinopathy (DR) is a microvascular consequence of diabetes. Even in the early stages of diabetic retinopathy, oxidative stress can cause damage to retinal vascular endothelial cells. However, in individuals with early-stage DR, effective care is required before the disease progresses to the more serious sight-threatening proliferative stage. This study explores the potential of nutraceuticals in the treatment of DR, focusing on their mechanisms of action as supported by evidence, clinical studies, and commercially accessible formulations. A thorough literature review was conducted to identify relevant research papers and reviews on nutraceuticals for the treatment of diabetic retinopathy. Relevant papers were located using scientific databases such as PubMed, Google Scholar, Elsevier, MDPI, ScienceDirect, and Web of Science. The search includes publications published up to November 2024 that used the standard keywords "Diabetic Retinopathy," "Nutraceuticals," "Evidence-Based Management," "Current Treatments," "Prevention," "Experimental Evidence," "Mechanisms of Action," "Marketed Formulations," "Clinical Studies," and "Future Directions." Nutraceuticals, which are natural functional foods with little adverse effects, have been advocated as therapeutic to people with DR. Many studies, both *in vitro* and *in vivo*, have established the benefits of a variety of nutraceuticals in DR, including their antioxidative, anti-inflammatory, neuroprotective, and vasoprotective activities. However, just a few clinical trials have been done, with varying results. Nutraceuticals, which combine natural ingredients with pharmaceutical chemicals, offer therapeutic potential in pathological situations such as DR. Although the findings are confined to animal models and have little bioavailability, they might provide a natural alternative to conventional therapies. Nutraceuticals may protect neurones, enhance retinal function, and activate pathways such as NF-κB and HIF-1α signalling. Diabetes-induced oxidative stress has been shown to increase inflammation and neurodegeneration, resulting in VEGF overexpression and vascular damage. Regardless of its preclinical character, research into interventive nutraceutical treatment may provide encouraging results in clinical applications.

Keywords: Diabetic retinopathy; Nutraceuticals; Evidence-based management; Current treatments; Prevention; Experimental evidence; Mechanisms of action; Marketed formulations

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Introduction

Nutrition is critical in managing diabetes development and consequences. Optimizing glycemic and lipid management is one of several first-line therapies in diabetes, reducing the development of DR [1]. Nonetheless, we will focus on antioxidant-rich particular meals and supplements providing an adjuvant treatment to the standard diabetic management [2].

Specific advice on food, its components, or other nutraceuticals that exert their effects upon type II diabetic mellitus (T2DM) may have been evaluated [3]. For example, very low-calorie diets (VLCD) have been demonstrated to be beneficial for weight and glycemic management for people with T2DM [4].

Further elements of an ordinary diet worth considering that have been previously explored with DR are the rise in polyunsaturated fatty acids (PUFAs), which at first are connected with lower prevalence and development of the disease [5]. Moderate alcohol intake, particularly white and complicated wines, has been researched with ambiguous results on the consequences in DR compared to different cohorts; as well as progressive studies reveal no relationship between their use and the start or advancement of DR [6].

Additionally, high sodium intake, a crucial component of the Dietary Pattern for the Prevention of Hypertension (DASH) diet, could have been related to the progression of DR, showing correlation among individuals alongside type I diabetes mellitus (T1DM), despite not showing a connection in other progressive studies or among patients with T2DM [7]. Consumption of carbohydrates alone has been demonstrated not to be related to DR, highlighting the significance for comprehending the pathophysiological processes involved in the beginning and advancement of DR, suggesting that this treatment requires an alternative strategy than diabetes management alone [8].

A wide range of nutritional supplements, phytochemicals, vitamins, as well as minerals containing antioxidant and/or anti-inflammatory characteristics have been found to have an important role in both the beginning and the development of DR. Some have been explored as solo treatments and others as combination therapies, most likely because they are on various points of some, along with most, of the pathways implicated in DR [9].

Nutraceuticals

Nutraceuticals are nutritional components encountered naturally throughout foods that are thought to provide health advantages. Dr. Stephen DeFelice coined the concept in 1989, combining the words "nutrition" with "pharmaceutical." These compounds, which include vitamins, minerals, amino acids, in addition to botanicals, are usually eaten in pill, capsule, or liquid form and are designed to complement the diet, prevent disease, or promote health. Nutraceuticals are frequently referred to as "functional foods" since they are scientifically produced to give health advantages beyond simple nourishment (Figure 1) [10].

Even though nutraceuticals are similar to dietary supplements, they vary in that they are expressly meant for disease prevention through treatment, rather than just augmenting nutritional consumption [11]. Pharmaceuticals, on the other hand, are medications that are intended to treat diseases and must go through rigorous clinical testing as well as patent protection. Nutraceuticals, in comparison, have less severe regulatory criteria, allowing for speedier development but occasionally missing the scientific confirmation of medicines [12].

Nutraceuticals have grown in popularity in recent years, with more studies confirming their advantages in areas

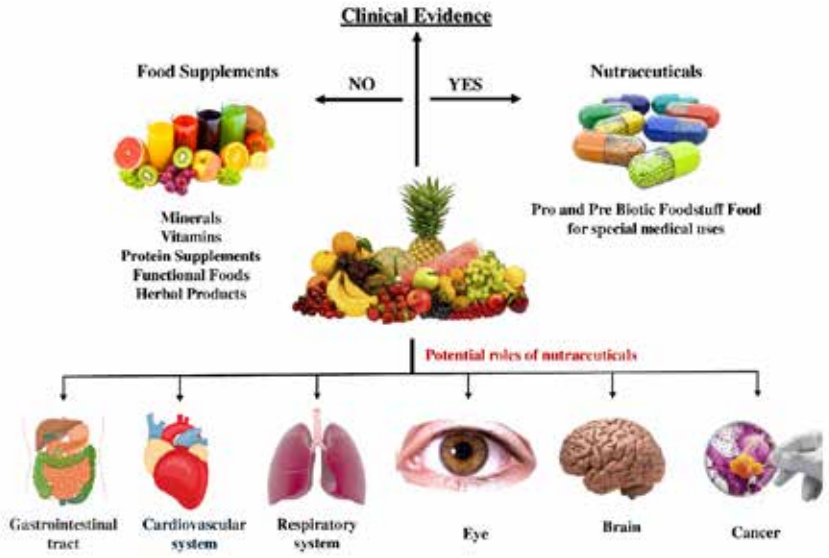


Figure 1. An overview regarding the many forms of nutraceuticals, including their applications [16].

including anti-aging, skin health, as well as chronic illnesses, including diabetes, arthritis, and heart disease [13]. As the sector develops, there is a drive for standardization and clinical trials to demonstrate its efficacy [14]. Nutraceuticals are currently a vital aspect of alternative medical treatments (CAM), and their relevance continues to expand within the larger healthcare landscape [15].

Using Nutraceuticals to Manage Diabetic Retinopathy

Diabetic retinopathy (DR) is a complex neuro-microvascular disease, whose incidence ranges from 25% to 60% of persons afflicted by diabetes mellitus, being the primary cause of legal blindness in adults in industrialized nations [17]. The therapy of severe stages of DR is centered on invasive and costly medicines, whereas few options are available for treating the initial stages or prevention [18]. The processes behind DR entail a complicated interplay between the negative effects of hyperglycemia, dyslipidemia, hypoxia, including oxidative stress, giving numerous routes potentially addressed by nutrients and nutraceuticals [19].

As previously stated, nutraceuticals have shown various advantages in ocular illnesses. Since the beginning of the twentieth century, genistein alongside other flavonoids, including luteolin especially fisetin, have shown promising outcomes in ocular diseases the context of rabbit models, there was a significant inhibition of corneal neovascularization after using a microemulsion along with topically administering flavonoids (luteolin: 0.5 mg/mL, genistein: 0.5 mg/mL, fistein: 1 mg/mL) [20]. These landmark discoveries have given impetus to continued study on the formulation of ophthalmology. Additionally, although prevention was not accomplished, it has been proven that genistein (15 mg/kg) supplied orally has the capacity to inhibit the formation of cataracts in rats [21].

Caffeic acid, some non-flavonoid compound, had been managed intraperitoneally (10 μmol/kg) with rats with generated uveitis from a lipopolysaccharide (LPS) injection in addition topically (25 μL to feed six hours every 30 min) throughout rabbits with paracentesis-induced discomfort of the anterior chamber along with reported beneficial effects in the attenuation about ocular inflammation as well as oxidative stress [22].

Alongside rat models alongside drug-induced ocular toxic effects, caffeic acid (10 μmol/kg) administered intraperitoneally increased the level of expression of essential enzymes accountable for controlling excessive oxidative stress, such as superoxide dismutase (SOD). This resulted in a substantial decrease in overall oxidant status and demonstrated the impact of this non-flavonoid substance on ocular stability [23]. Furthermore, the function of the intraperitoneally injected caffeic acid (10 mg/kg) within mitochondrial processes has been demonstrated in mice by the decrease of ROS through the separating protein (UCP2), resulting in the continued existence of the retinal pigment epithelium cells [24].

A powdered diet containing eicosapentaenoic acid (EPA; 650 mg), α lipoic acid (750 mg), vitamin C (300 mg), benfotiamine (1 g), vitamin D3 (10,000 IU), fish oil EE70% (1.6 g), vitamin E (300 IU), docosahexaenoic acid (DHA; 500 mg), lutein (20 mg), tocomin (200 mg), ze [25]. Nutraceuticals are natural food products that provide medicinal or health advantages. Certain nutraceuticals, including carotenoids, are powerful antioxidants with the ability to scavenge ROS. Some have anti-inflammatory properties and may influence NF-κB expression [26]. Several nutraceuticals have been demonstrated to improve neuronal and microvascular functioning [27]. Nutraceuticals are natural foods, are widely available and reasonably priced. Furthermore, adequate dietary supplementation with nutraceuticals is thought to be safe and less likely to generate adverse effects common to many anti-diabetic medicines, such as hypoglycemia, complications of kidney and liver damage, and gastrointestinal discomfort [28].

Finally, nutraceuticals have been shown to improve diabetic retinopathy (DR). Preclinical investigations in diabetic-induced mice have demonstrated to avoid the development of ROS and to enhance visual function by reducing the visual impairment caused by diabetes and measured by electroretinograms upon adding lutein (0.1%) to their regular diet [29].

Diabetic Retinopathy: Evidence-Based Management

The World Health Organization (WHO), the American Academy of Ophthalmology (AAO), and the Royal College of Ophthalmologists have established evidence-based guidelines for the screening, diagnosis, and treatment of diabetic retinopathy (DR). These guidelines emphasize the need for individualized treatment based on a patient's specific risk factors, including glycemic control, blood pressure regulation, and disease severity.

To prevent the onset and progression of DR, the guidelines strongly recommend maintaining optimal blood glucose (HbA1c < 7%) and blood pressure levels. The importance of these measures is supported by major clinical trials, such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), which demonstrated that strict glycemic and blood pressure control significantly slows DR progression [30].

Screening for DR is crucial for early detection, with dilated fundus examination being the primary method to identify vascular abnormalities in the retina. Additionally, ocular imaging techniques such as fundus photography and optical coherence tomography (OCT) are widely used to detect early DR manifestations, including cotton-wool spots and microangiopathy [31].

Given that DR progression varies among patients, several studies have investigated personalized screening intervals based on individual risk factors such as glycemic control, DR severity, and cost-effectiveness of screening programs [32, 33]. For instance, an Australian clinical trial found that patients with poor blood pressure or choles-

terol management and inadequate glucose control were at a significantly higher risk of DR progression. This research supports the idea that screening intervals should be adjusted based on individual risk rather than following a fixed annual schedule [34]. Most studies recommend a screening interval of one to two years, particularly for patients with well-controlled diabetes [35].

Early detection through regular photographic screening is an effective strategy for preventing vision loss [36]. The Canadian Diabetes Association (CDA) guidelines recommend that patients with Type 1 Diabetes Mellitus (T1DM) undergo eye examinations starting at age 15, five years after diagnosis, while those with T2DM should be screened immediately upon diagnosis [37]. Furthermore, national guidelines advise annual dilated fundus examinations for all diabetes patients, regardless of whether they present with ocular symptoms [38]. This approach balances the need for early intervention while optimizing healthcare resources.

The impact of DR on quality of life is well-documented. An Australian study found that reduced visual acuity in the better eye due to DR was associated with poorer functional and psychological well-being [39]. Another study revealed that self-reported vision loss in DR patients was linked to emotional distress, limitations in daily activities, and reduced social engagement [40]. These findings highlight the importance of timely intervention to preserve vision and maintain overall well-being.

Diabetic retinopathy is classified into two stages:

1. Non-proliferative DR (NPDR) is an early stage where vascular abnormalities develop but may not yet cause vision impairment. However, macular edema at this stage can significantly affect vision.
2. Proliferative DR (PDR) is an advanced stage characterized by the rapid growth of abnormal retinal blood vessels, increasing the risk of retinal detachment and severe vision loss [41].

For patients with diabetic macular edema (DME), the first-line treatment consists of intravitreal anti-VEGF therapy using bevacizumab, pegaptanib, ranibizumab, or aflibercept. Several clinical trials have confirmed that these treatments are highly effective in reducing retinal neovascularization and improving vision [42].

For advanced DR, laser photocoagulation remains a gold-standard treatment. Techniques such as panretinal photocoagulation (PRP), focal macular laser therapy, and grid photocoagulation effectively reduce disease progression by targeting abnormal, leaking blood vessels [43]. In cases of vitreous hemorrhage, tractional retinal detachment, or fibrovascular proliferation, pars plana vitrectomy is the preferred surgical intervention to prevent permanent vision loss (Figure 2) [44].

The provided examples demonstrate how clinical studies, screening recommendations, and treatment modalities directly contribute to evidence-based DR management. By implementing personalized screening schedules, maintaining glycemic and blood pressure control, and utilizing modern therapeutic interventions, the risk of severe vision loss from DR can be significantly reduced.

Nutraceuticals and Diabetic Retinopathy: Prevention and Treatment

Despite several studies attempting to find potential medications for both prevention and therapy of DR, nutraceuticals have received very little attention. Nutraceuticals are naturally functional foods that promote different health advantages. They comprise a variety of substanc-

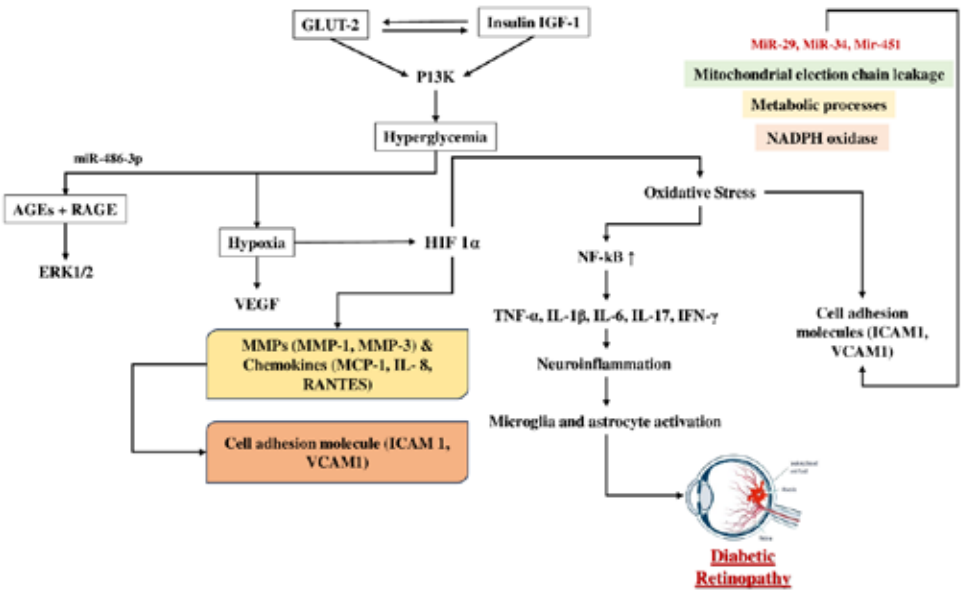


Figure 2. The above piece provides an overview of the NF-κB pathway, which is crucial to the occurrence of diabetic retinopathy. Red bubbles include miRNAs, which can play an essential part in targeting certain nodes [45,46].

es, including vitamins, antioxidants, minerals, omega-3 fatty acids, and amino acids that help prevent or postpone the course of certain illnesses [47]. Several studies have demonstrated that nutraceuticals have diverse therapeutic advantages and can protect against a variety of ailments. The consumption of nutraceuticals in diabetes helps to increase insulin sensitivity, regulate metabolism, and reduce hyperglycemia.

Flavonoids, as well as carotenoids, have been shown to have substantial antioxidant and anti-inflammatory activities [48]. Several animal models, along with human studies, have shown that flavonoids, a large family of compounds obtained from plants, may decrease or attenuate complications associated with diabetes by modulating lipid and carbohydrate metabolism along with insulin resistance, mitigating hyperglycemia, and suppressing oxidative stress along with inflammatory processes [49].

Vitamins and overall nutraceuticals immediately improve blood vessel flexibility and metabolism. Antioxidants are thought to protect the organism against free radicals and nitric oxide against inactivation [50]. Oxidative stress occurs when the concentration of reactive oxygen species exceeds the effectiveness of antioxidant buffers. Oxidative stress tests can detect hypertension, arterial disease, and diabetes during an early stage.

Typically, nitric oxide improves vascular health by modulating vascular tone (vasodilation), decreasing platelet activity, and blocking leukocyte adhesion [51]. Reduced nitric oxide levels cause endothelial dysfunction, which leads to inflammation, vasospasm, and thrombosis. Vitamins C and E, for example, act as antioxidants and reduce oxidative stress by raising nitric oxide levels. They also neutralize the peroxidation of lipid byproducts, which damage cell membranes [52].

Figure. 3 numerous research investigations have demonstrated that consuming vitamins C, D, E, B1, folate, B12, lipoic acids, lutein, N-acetyl cysteine, and overall betaine can improve endothelial function, neuroprotection, blood pressure control, and visual acuity. The retina receives these advantages [53].

Retinopathy is still among the most serious consequences of diabetes. Despite significant progress in fundamental science and clinical studies to comprehend the complicated pathophysiology associated with this blinding illness, the precise mechanism remains obscure, and viable treatment approaches are uncertain [55].

Diabetes causes increased oxidative stress in both the retina, including capillary cells, resulting in mitochondrial malfunction and damage to mitochondrial DNA (mtDNA). Along with capillary cells, increased oxidative stress has been seen in other retinal cells, especially photoreceptors as well as retinal pigment epithelial cells [56]. Supplementing diabetic rats with antioxidants such as lipoic acid, multi-antioxidants, or AREDS-based antioxidants reduces the development of diabetic retinopathy [57].

Nutraceutical supplementation protects against diabetic retinopathy while also maintaining normal retinal functioning, mitochondrial homeostasis, and reduced inflammatory mediators [58]. Thereby, this supplementation might offer a feasible and affordable supplemental therapy to block retinopathy, a slow-progressing illness that diabetes patients fear more than anything [59].

Nutraceuticals have, and their metabolites are increasingly being used to treat a wide range of disorders [60]. Natural extracts are becoming increasingly popular as al-

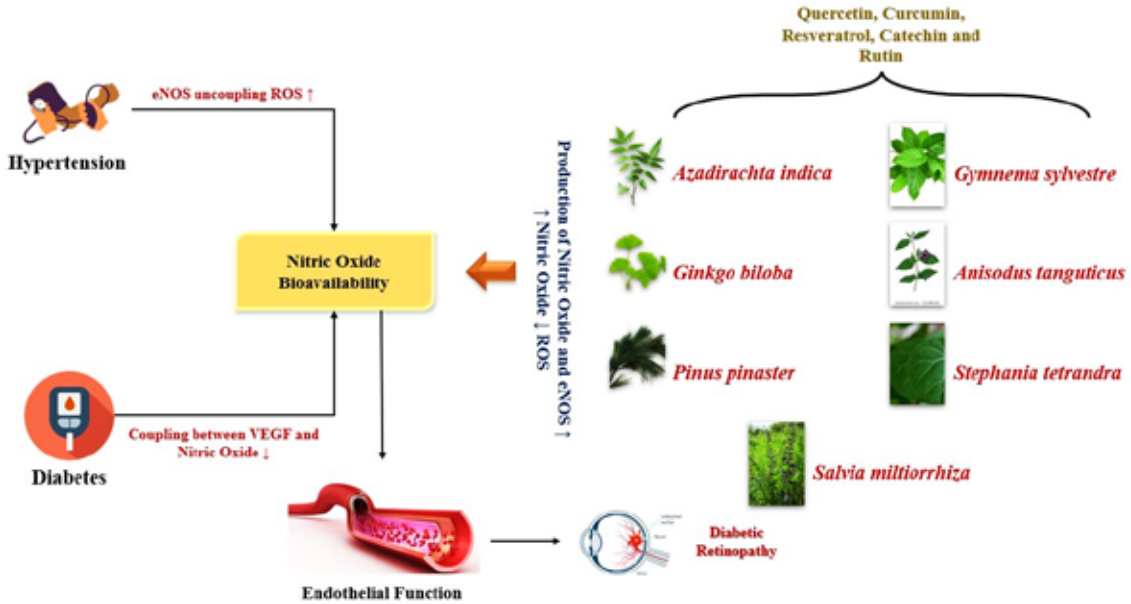


Figure 3. The impact of nutraceuticals on arterial endothelial function during systemic vascular disorders. Endothelial nitric oxide synthase (NOS) or reactive oxygen species (ROS), VEGF is vascular endothelial growth factor; NAC: N-Acetyl Cysteine [54].

ternative therapy techniques for DR. Every category of NPs is explored separately regarding their protective role in DR (Table 1) [61].

Antioxidants and Retinal Protection

Oxidative stress plays a major role in retinal damage in diabetes. Antioxidants neutralize free radicals, reducing cellular damage and inflammation.

Flavonoids

Mechanism: Flavonoids protect against oxidative stress and vascular damage by scavenging free radicals and enhancing blood flow in the retina.
Evidence: Studies indicate that flavonoids inhibit VEGF, reducing retinal neovascularization, a hallmark of proliferative DR.
Sources: Green tea (catechins), citrus fruits (hesperidin), berries (anthocyanins).

Carotenoids (Lutein & Zeaxanthin)

Mechanism: These xanthophylls accumulate in the macula, where they absorb blue light, reducing light-induced oxidative stress and inflammation.
Evidence: Research shows that higher dietary lutein and zeaxanthin levels lower the risk of DR progression.
Sources: Spinach, kale, broccoli, corn, egg yolk.

Vitamin C (Ascorbic Acid) & Vitamin E (Tocopherol)

Mechanism:
Vitamin C regenerates glutathione, reducing oxidative damage in the retina.
Vitamin E protects polyunsaturated fatty acids in retinal cell membranes from lipid peroxidation.
Evidence: Studies suggest that higher plasma vitamin C levels correlate with a lower risk of DR, while vitamin E may enhance retinal microvascular health.
Sources:
Vitamin C: Citrus fruits, bell peppers, strawberries.
Vitamin E: Nuts, seeds, spinach, sunflower oil.

Anti-Inflammatory and Neuroprotective Nutrients

Chronic inflammation in diabetes damages retinal neurons and blood vessels, leading to retinal edema and ischemia.

Omega-3 Fatty Acids (EPA & DHA)

Mechanism: Omega-3 fatty acids reduce inflammation by inhibiting pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) and decreasing vascular permeability.
Evidence: Clinical trials indicate that higher dietary intake of omega-3 fatty acids is linked to lower DR risk and improved retinal function.
Sources: Fatty fish (salmon, mackerel), flaxseeds, walnuts, chia seeds.

Curcumin (Turmeric Extract)

Mechanism: Curcumin modulates NF-κB and COX-2 pathways, reducing inflammatory cytokines in the retina.
Evidence: Animal studies show curcumin protects against DR-related microvascular damage and reduces oxidative stress.
Sources: Turmeric (best absorbed with black pepper due to piperine).

Nutrients for Vascular Health and Blood Sugar Control

DR is worsened by poor blood circulation and hyperglycemia, which leads to retinal ischemia and microvascular damage.

Magnesium

Mechanism: Magnesium helps regulate blood vessel dilation, improves insulin sensitivity, and reduces inflammation.
Evidence: Studies show magnesium deficiency is associated with higher DR severity and worse glycemic control.
Sources: Leafy greens, nuts, seeds, whole grains.

Zinc

Mechanism: Zinc plays a role in retinal cell function by supporting antioxidant enzymes (superoxide dismutase) and reducing oxidative stress.
Evidence: Zinc supplementation has been shown to protect retinal capillary cells from hyperglycemia-induced damage.
Sources: Shellfish, meat, pumpkin seeds, and lentils.

B Vitamins (B1, B6, B12, Folate)

Mechanism: These vitamins regulate homocysteine levels, a compound linked to retinal vascular dysfunction and capillary leakage.
Evidence: Higher B-vitamin intake is associated with lower DR prevalence in some population studies.
Sources: Whole grains, eggs, dairy, legumes, and meat.

Blood Sugar Modulation and Insulin Sensitivity

Maintaining stable blood glucose levels is crucial to preventing DR progression.

Chromium

Mechanism: Enhances insulin sensitivity and glucose metabolism by activating insulin receptors.
Evidence: Studies show chromium supplementation reduces HbA1c levels, which may slow DR progression.
Sources: Broccoli, whole grains, nuts, and meat.

Alpha-Lipoic Acid (ALA)

Mechanism: ALA is a powerful antioxidant that improves mitochondrial function, reduces oxidative stress, and enhances insulin sensitivity.
Evidence: Clinical studies suggest ALA supplementation reduces oxidative damage in diabetic patients, potentially slowing retinal degeneration.
Sources: Spinach, broccoli, tomatoes, red meat.

Several clinical studies have investigated the effects of nutritional and pharmacological interventions in diabetic retinopathy (DR). For example, the use of anti-VEGF inhibitors (bevacizumab, ranibizumab, aflibercept) has been extensively studied, with results indicating a significant reduction in retinal neovascularization and macular edema. In a study by Nguyen et al. (2012), patients receiving intravitreal ranibizumab (0.3 mg monthly for 24 months) demonstrated a 10-letter improvement in visual

acuity compared to the control group.
Similarly, antioxidant therapy with lutein and zeaxanthin (10 mg and 2 mg daily, respectively, for 12 months) has been shown to increase macular pigment density and reduce oxidative stress markers in DR patients. In contrast, omega-3 fatty acids (1.8 g/day for 6 months) were found to reduce inflammatory cytokines (IL-6, TNF-α) and improve retinal microvascular function.

1. *Quercetin*

Diabetes mellitus produces neuropathy and retinopathy, posing major health risks. Quercetin, a flavonoid present in fruits and vegetables, has demonstrated potential therapeutic advantages for its antioxidant, anti-inflammatory, and potentially neuroprotective characteristics [62]. Preclinical investigations indicate that quercetin can reduce neuropathic pain, sensory impairments, and nerve damage during diabetic neuropathy by increasing neuronal function, lowering DNA damage, and healing nerve injuries [62]. Regarding diabetic retinopathy, it maintains retinal form and function by altering critical signaling pathways [63].
Diabetic retinopathy (DR) is a frequent ocular consequence of diabetes that endangers patients' vision and causes blindness in the majority of working-age persons in industrialized nations. Quercetin (3, 3′, 4′, 5, 7-pentahydroxy flavonoids) constitutes a natural polyphenol found in many fruits and vegetables. It has a variety of biological functions, including the prevention of oxidation, inflammation, tumors, and angiogenesis [64]. It was believed that quercetin might have beneficial effects in RNV [65].
Quercetin, a naturally occurring flavonoid with several biological functions, is extensively dispersed throughout plants. Quercetin is well known for its antioxidant effects [66]. It has recently been shown to have anticancer properties, as well as to enhance cognitive and cardiovascular function [67]. Quercetin's actions may be due in part to its activation of heme oxygenase-1 (HO-1). However, the significance of quercetin during DR, as well as the underlying processes remain unclear [68].

Evidence from experiments and mechanisms of action

The study found that quercetin has potential for therapy in DR by suppressing retinal endothelial cell dysfunction during high-glucose (HG) circumstances. Quercetin efficiently inhibits angiogenesis, as seen by reduced cell survival, migration, and increased tube formation among human retinal microvascular endothelial cells (HRMECs) injected with HG. Quercetin inhibits the activation of the NLRP3 inflammasome, resulting in reduced expression of the proteins NLRP3, ASC, Caspase-1, as well as the inflammatory cytokines IL-1β and IL-18. Furthermore, quercetin suppresses autophagy, as indicated by lower expression of autophagy markers LC3 as well as Beclin-1, as well as decreased autophagic activity. The inhibitory impacts of quercetin on the two NLRP3 inflammasome activation and phagocytosis appear to have been concentration-dependent, with larger doses having a greater impact. These data indicate that quercetin may be a viable therapeutic treatment for DR, notably in modifying retinal angiogenesis, inflammation, and autophagy via the NLRP3 inflammasome pathway. Further research is needed to explain the specific molecular pathways and to investigate its therapeutic usefulness in controlling DR [69].
Quercetin, an internationally recognized antioxidant, could help protect against damage caused by oxidative stress during diabetic retinopathy (DR). It has been demonstrated to reduce the expression of HMGB1 in sepsis, tumors, and cardiac ischemia-reperfusion damage. In DR, HMGB1 activates NF-κB and causes oxidative stress. Quercetin inhibits the induction of the HMGB1/TLR4/NF-κB/NLRP3 inflammasome/IL-1β/IL-18 axis in a HO-1-dependent way. It also reduces VEGF expression and inhibits the release of VEGF and sICAM-1 in a HO-1-dependent way. The study discovered that quercetin boosted retinal cell layer thickness, ganglion cell counts, and reduced pro-inflammatory markers. It also suppressed TLR4 and NF-κBp65 expression, decreased the amount of vascular endothelial growth factor expression, and increased neurotrophin levels. The protective effect of quercetin was linked to its anti-inflammatory, anti-angiogenic, and neurotrophic properties. The study reveals that quercetin's therapeutic promise in DR is based on its anti-inflammatory, anti-angiogenic, and neurotrophic properties. Quercetin, a flavonoid, was reported to have therapeutic benefits on DR in rats [70].
The study looks at the nano-formulation with quercetin (NQ) using a zebrafish model that represents DR. Streptozotocin (STZ) was administered intraperitoneally to speed the DR process. NQ therapy was given for 21 days in a row, compared to a reference medicine, dexamethasone (DEX). The findings revealed that NQ reduced the impact of STZ-induced DR and controlled metabolic abnormalities in a manner comparable with that of the DEX-treated group. NQ may be used to treat diabetic retinopathy including neurosensory problems [71].
This study looked at how quercetin affected the levels plasma monocyte chemoattractant protein (MCP)-1, matrix metalloproteinase (MMP)-9, and VEGF in the serum of animals with diabetic retinopathy. 20 rats suffering from induced diabetes were split into two groups: model and quercetin, each consisting of ten animals. Quercetin was given intragastrically, and sodium carboxymethyl cellulose was employed in both groups. In diabetic rats, blood glucose testing revealed that quercetin did not lower blood glucose levels. However, it may alleviate pathological alterations associated by diabetes, including retinal oedema and vacuoles. The study indicates that quercetin has a therapeutic impact on diabetic retinopathy

Table 1. Summary of Treatment Effects in Diabetic Retinopathy

Sr No.	Treatment	Dose	Duration	Main Effects
1.	Anti-VEGF (Ranibizumab)	0.3 mg intravitreal injection, monthly	24 months	↑ Visual acuity (+10 letters), ↓ Macular edema
2.	Lutein & Zeaxanthin	10 mg + 2 mg daily (oral)	12 months	↑ Macular pigment density, ↓ Oxidative stress
3.	Omega-3 Fatty Acids	1.8 g/day (oral)	6 months	↓ Inflammatory markers (IL-6, TNF-α), ↑ Retinal microvascular health
4.	Curcumin	500 mg twice daily (oral)	8 months	↓ Retinal inflammation, ↑ Neuroprotection
5.	Quercetin	50–100 mg/kg/day (oral)	8–12 weeks	↓ Oxidative stress, ↓ Retinal inflammation, ↑ Antioxidant enzyme activity
6.	Resveratrol	5–10 mg/kg/day (oral)	6–12 weeks	↓ Retinal vascular damage, ↓ Apoptosis of retinal cells
7.	Catechin	200 mg/day (oral)	10 weeks	↓ Vascular permeability, ↑ Retinal microvascular health
8.	Rutin	50–100 mg/day (oral)	12 weeks	↓ Capillary leakage, ↑ Retinal antioxidant defenses

by lowering MMP-9 as well as VEGF expression, while not inhibiting MCP-1 (Figure 4) [72].

Quercetin has been extensively researched in the field of ophthalmology because to its potent antioxidant, anti-inflammatory, immunomodulatory, anti-carcinogenic, vascular protection, neuroprotection, and numerous other biological properties. It is anticipated to function as a potentially beneficial treatment medication for ocular illnesses. However, most investigations concentrated on in vitro and in vivo (animal model) trials. Due to insufficient information in human research, there is still significant work to be done to evaluate the clinical applicability of quercetin in ophthalmology [74].

2. *Curcumin*

Diabetic retinopathy (DR) constitutes a retinal microangiopathy induced by diabetes mellitus that causes blindness in people working across the world. Treatment options include vitrectomy, retinal photocoagulation, including anti-vascular endothelial growth factor (VEGF) medication [75]. Curcumin's anti-apoptotic, anti-inflammatory, antioxidant, as well as anticancer effects have long been employed in traditional Chinese medicine. Nevertheless, curcumin's preventative and therapeutic benefits on DR,

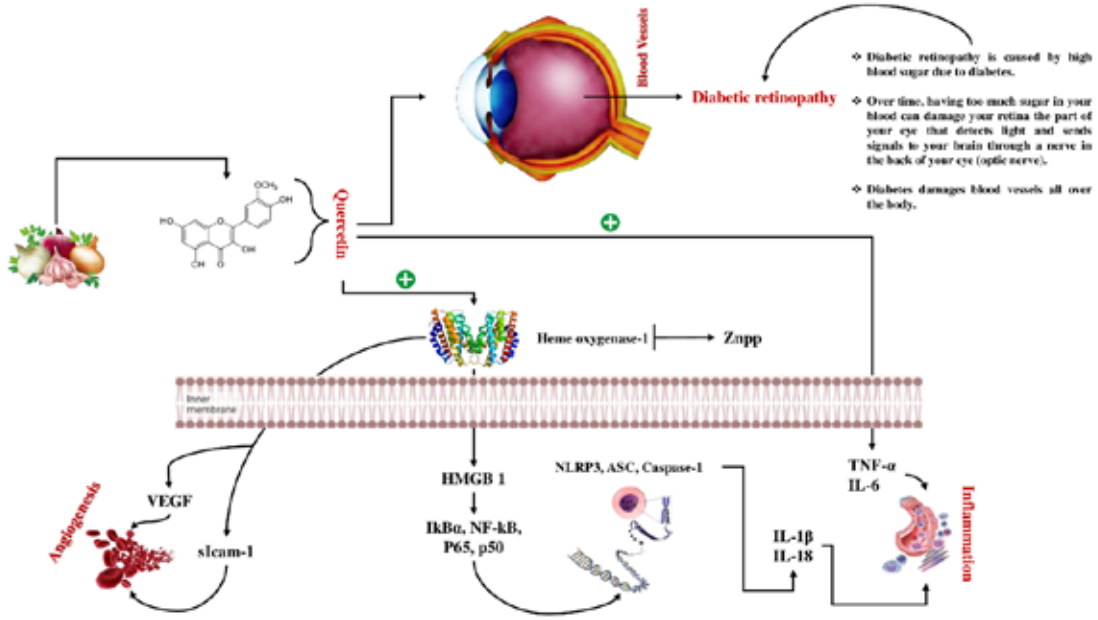


Figure 4. Experimental research shows that quercetin protects against diabetic retinopathy. Quercetin alters critical processes involved in inflammation as well as oxidative stress, hence increasing retinal function and lowering vascular damage. These findings reveal a possible treatment strategy in diabetic retinopathy [73].

as well as its mechanisms of action, have yet to be thoroughly understood [76]. Curcumin has been shown to enhance glucose and lipid metabolism, insulin sensitivity, insulin resistance, and oxidative stress, in addition to inflammatory pathways in diabetes and DR. Curcumin is the primary ingredient of turmeric [77].

Curcumin, additionally to being widely recognized as a spice, offers several medicinal benefits. As an anticancer drug, it may prevent ovarian, prostate, breast, and stomach cancers, among others [78]. In addition, curcumin has anti-inflammatory properties and can be utilized for the management of chronic obstructive pulmonary disease (COPD), hepatic inflammation, and even acute vascular inflammation [79].

Curcumin, which is a natural antioxidant, has been shown to have renoprotective properties. In rats with diabetes, particularly Müller cells, increased histone acetylation is critical for regulating the inflammation response [80]. Curcumin can protect against diabetes by reducing histone acetylation. Curcumin's preventative and curative benefits on DR, as well as its mode of action, have yet to be fully elucidated [81].

In vitro research has also shown that curcumin protects cells against high-glucose environments [82]. In the year a study that exposed insulin (INS)-1 cells to elevated amounts of glucose in addition to or without curcumin, the development of INS-1 cells, morphological alterations of islet cells, the production of reactive oxygen species (ROS), the activities regarding superoxide dismutase along with catalase, insulin levels, the gene expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits, in addition to the expression of apoptotic factors were all observed [83].

Similarly, several researchers discovered that curcumin can drastically lower fasting blood glucose among diabetic mice. Curcumin treatment in rats resulted in minor pancreatic tissue damage and lowered expression levels of IL-1, IL-6, MCP-1, TNF-α, Bax, and caspase-3 [84]. These findings suggest that curcumin can reduce pancreatic islet cell death and inflammation while also improving pancreatic function [85]. Further clinical trials may investigate curcumin's bioavailability as well as regulatory effects upon autophagy and apoptosis, offering insight into the development of innovative treatments for DR [86].

Evidence from experiments and mechanisms of action

Curcumin has been shown to offer potential therapeutic effects for diabetic retinopathy. The study included diabetic rats using blood glucose levels ≥11.6 mmol/L, separated into three distinct categories: diabetic rats without therapy, diabetic rats with curcumin, and diabetic rats administered curcumin. The rats were then investigated for retinal histology, ultrastructural alterations, and antioxidant activity. Curcumin was found to lower blood glucose levels, prevent diabetes-induced weight loss, and improve diabetes-induced retinal abnormalities. Curcumin demonstrated a considerable antioxidant activity throughout the retina, suppressing VEGF expression while upregulating Bcl-2 along with Bax expression [87]. The study sought to determine the therapeutic efficacy of oral curcumin in preventing and curing streptozotocin-induced diabetic retinopathy using Wistar albino rats. The therapy lasted 16 weeks and measured hyperglycemic, antioxidant, and inflammatory markers. The results demonstrated considerable hypoglycemic activity relative to the diabetic group, a 1.5-fold drop in retinal glutathione levels, and an increase in antioxidant enzymes. Curcumin improved the antioxidant system and inhibited the rise of proinflammatory cytokines within diabetic retinas. The study also discovered degradation of endothelial cell organelles as well as increased capillary basement membrane thickness among diabetic retinas. The data indicate that curcumin might possess potential advantages in avoiding retinopathy in diabetic people [88].

The present therapy for DR includes anti-inflammatory medicines, laser photocoagulation, and anti-angiogenesis pharmaceuticals, although these procedures can harm retinal structures and impair visual function. A secure and beneficial technique is required to manage or postpone DR. Curcumin, a turmeric ingredient, has been demonstrated to have antioxidant, anti-inflammatory, and nuclear transcription factor inhibitory properties, potentially preventing or delaying DR development. Curcumin's ability to modulate gene function indicates a unique treatment method for DR prevention. Turmeric and its ingredients are safe, efficient, and inexpensive, making them essential for treating diabetes and its consequences. Curcumin's potential for preventing DR is promising [89].

Diabetic retinopathy is a frequent microvascular consequence of diabetes that includes defective retinal pigment epithelium, interretinal oedema, and intraocular neovascularization. This study investigates the antioxidant and anti-inflammatory activities of curcumin extract from Curcuma longa in relation to diabetes-induced retinal vascular injury. Curcumin promotes Brn3a expression under oxidative stress, which raises retinal ganglionic cells while lowering inflammatory mediators. Curcumin looks to be a beneficial adjuvant therapy to potentially prevent the progression of acute retinopathy, a vision-threatening condition for diabetic patients [90].

Diabetic retinopathy constitutes a serious microvascular condition associated with type 1 as well as type 2 diabetes. Hyperglycemia induces vascular endothelial growth factor (VEGF), which influences the pathophysiology. A study discovered that curcumin, as well as turmeric, can reduce VEGF expression in diabetic rat retinas. The study discovered a rise in VEGF expression within diabetic retinas, which curcumin and turmeric suppressed. This implies that dietary components can prevent and cure diabetic retinopathy [91].

Curcumin was reported to lower reactive oxygen species (ROS) and prevent apoptosis when RRVECs were

exposed to high glucose levels. It effectively inhibited NF-κB activity and phosphorylation in RRVECs generated through high glucose concentration, protecting them from DR [92].

A painless therapy has been created employing surface-modified Curcumin PLGA nanoparticles. The nanoparticles were optimized and evaluated for drug release, sterility, histology, and isotonic properties. The formulation had good benefits in vivo, with a dose-dependent decrease in vascular endothelial growth factor concentration [93].

The study created ozonated liposomes loaded with curcumin for ocular medication delivery, intending to precisely treat diabetic retinopathy. The liposomes had a particle size of 84.77 nm, a zeta potential of -16.8 mV, and an encapsulation efficiency of 94.73%, making them promising for curcumin administration. Over the course of three months, the formulation showed very little change [94].

The major cause of microvascular difficulties in diabetics is oxidative stress, which occurs when aberrant metabolic circumstances boost superoxide generation in mitochondria as well as microvascular endothelial cells. High glucose levels cause overuse of NADPH, an important reactive oxygen species (ROS) scavenger, leading in increased ROS generation [95]. This causes an elevated inflammatory response throughout the nearby area. Curcumin has high antioxidant activity in DR, and its presence has been found to diminish ROS and endothelial cell death (Figure 5) [96].

Cytokines such as TNF-α can harm vascular endothelial cells, causing hypoxia and necrosis. Research has demonstrated that the presence of both inflammatory disorders and oxidative stress contributes to the development as well as progression of DR. Curcumin has been demonstrated to increase the efficiency of various antioxidants while also possessing high anti-inflammatory and protective characteristics [97]. Inhibiting the development of smooth muscle cells in the arteries and enhancing PPAR-γ activity can assist to lower NO production and inflammation. Curcumin may serve as an anti-inflammatory drug by lowering TNF-α levels along with preventing retinal cell damage induced by high glucose levels [98].

Curcumin's ability to scavenge ROS, along with additional free radicals, offers protection against oxidative stress. Curcumin reduced ROS and oxidative stress in adult retinal pigment epithelial cells (ARPE-19 cells) cultured in vitro while also restoring DNMT production and function. It also prevents protein kinase C (PKC), xanthine oxidase (XOD), and lipoxygenase (LOX) production. PKC, a critical oxidative stress factor, may contribute to DR development. Curcumin may partially inhibit PKC, decrease oxidative stress, and preserve retinal tissue, in accordance with several research [100, 101].

3. Resveratrol

Resveratrol (RSV) is a naturally occurring, physiologically active polyphenol that has been shown to offer a variety of health benefits in animal models and people [102]. Continuous use of synthetic medications frequently results in side effects, the need has shifted to non-/less-toxic herbal-derived pharmaceuticals for a variety

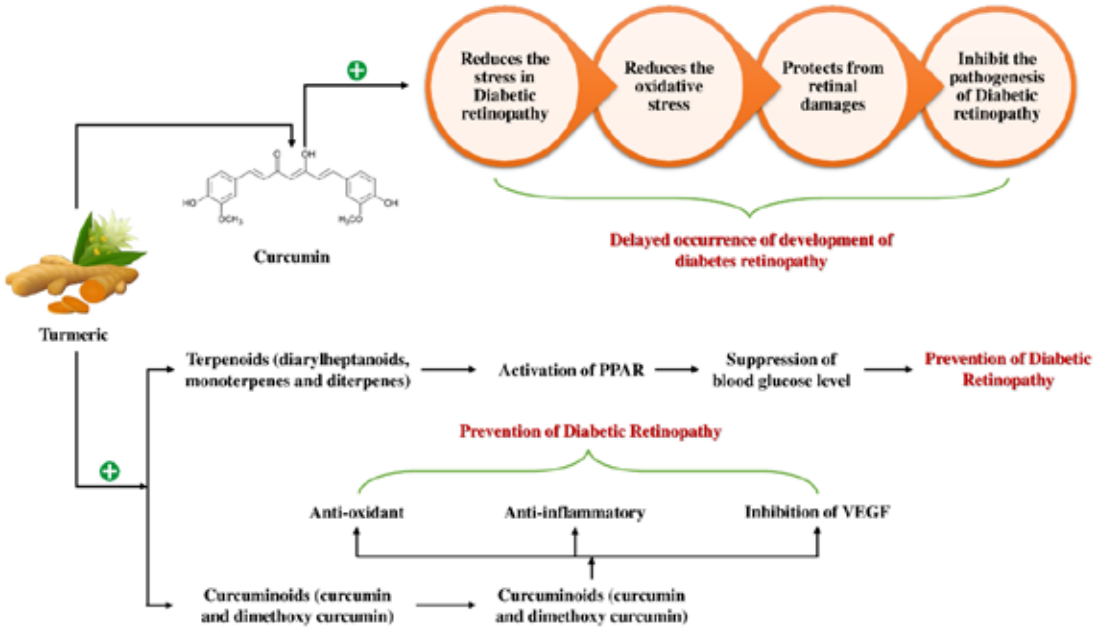


Figure 5. Curcumin's preventive impact in diabetic retinopathy is evidenced by its capacity to suppress inflammatory and oxidative stress pathways, hence reducing retinal damage and maintaining vascular function [99].

of conditions, including diabetes, cancer, non-alcoholic fatty liver disease (NAFLD), infection disorders, and inflammation-related diseases [103].

Nonetheless, just a few numbers have been tested to determine their effectiveness. Recent research clearly suggests that resveratrol (RSV) protects against diabetes and associated consequences. RSV's protective mechanisms involve several signaling pathways regulation, including inhibition of oxidative stress along with hyperinflammation, enhancement of insulin action, induction of autophagy, regulatory impact on lipid metabolism, increasing GLUT4 expression, along with activation of the Sirtuin 1 (SIRT1)/Adenosine Monophosphate Activated Protein Kinase (AMPK) signaling axis [104].

Resveratrol serves as a natural polyphenol with antioxidant and anti-inflammatory characteristics, and its effectiveness has previously been studied in a variety of disorders, including DR. We wanted to present a comprehensive understanding of the signaling pathways, including mechanisms of action via which resveratrol displays its effects on DR and its consequences [105].

Evidence from experiments and mechanisms of action

The study looked at the anti-ferroptotic effects of resveratrol (RSV) affecting retinal Müller cells (RMCs) throughout the early stages of diabetic retinopathy. The retina was collected from normal and diabetic Sprague-Dawley rats, as well as wild-type experimental Nrf2 knockout (KO) diabetic mice. RSV prevented retinal neurofunctional and mitochondrial morphological alterations, lowered Fe2+, MDA, and PTGS2, and raised GSH, Nrf2, and GPx4 in DM rats' retinas. In vitro, RSV reduced MDA and PTGS2 while increasing cell viability, GSH, Nrf2, and GPx4. The function of the Nrf2-regulated signaling pathway in RSV-induced antiferroptosis was verified using Nrf2 knockout animals and pre-transfected SiNrf2 in RMCs. These data show that RSV is a possible treatment option for DR and indicate that Nrf2/GPx4/PTGS2 plays a role in RSV's anti-ferroptosis mechanism affecting RMCs [106].

Current treatments rely on expensive anti-VEGF injections, which might have side effects. Nanostructured formulations improve medication delivery and penetration. Recombinant resveratrol nanosuspension (RSV-NS) was created and analyzed using light scattering, scanning electron field emission microscopy, as well as infrared spectroscopy. The nanosuspension exhibited a transparent appearance with particles smaller than 500 nm. Endothelial cells (HMRECs) were examined for viability, proliferation, and migration. At dosages below 18.75 μM, RSV-NS had no cytotoxic effects, although it did inhibit cell proliferation as well as migration. Future studies should focus on assessing the nanosuspension affecting stressed cells to imitate in vitro circumstances in DR, and investigating its influence on glucose levels or inflammatory cytokines [107].

The study looks at the protective processes and therapeutic advantages of Resveratrol (RSV) against diabetic retinal neurodegeneration. Researchers developed a diabetic mouse model and performed visual electrophysiological tests. The findings revealed that RSV considerably enhanced retinal architecture and function, decreased retinal ganglion cell death, and boosted protein expression of SLC7A11 as well as Nrf2. The study reveals that RSV may lower levels of oxidative stress in the retina and suppress retinal ganglion cell death by decreasing the Nrf2/HO-1 pathway, which minimizes the damage that results from excessive glucose [108].

According to the study, Resveratrol (RSV), a naturally occurring plant polyphenol, can suppress retinal Müller cells (RMCs) death by modulating miR-29b/SP1 expression. This is critical for the early detection and treatment of diabetic retinopathy. RSV was also observed to boost autophagosome formation, LC3-I/LC3-II, and Beclin-1 levels, while lowering P62 levels. This stimulates autophagy and suppresses the dysregulation underlying miR-29b/SP1 pathway expression, hence reducing DR development [109].

The study investigates the possibility of a nanosuspension (RSV-NS) containing resveratrol (RSV), a type of polyphenol exhibiting antioxidant activity, as a therapy for proliferative diabetic retinopathy. The proposed nanosuspension was evaluated using human microvascular retinal endothelial cells (HMRECs) to assess its anti-inflammatory and antiangiogenic properties. The results demonstrated that RSV-NS greatly lowered HMREC metabolic activity as well as proliferation while remaining non-cytotoxic. It also inhibited cell proliferation, migration, increased tube formation in a VEGF-stimulated in vitro model. The result implies that RSV-NS may be employed in future therapies to reduce pathological ocular angiogenic disorders [110].

The study examined how resveratrol administration affected oxidative stress, NF-κB activity, and apoptotic rate among male Wistar rats with streptozotocin-nicotinamide-induced diabetic retinopathy. Four months of oral resveratrol therapy reduced diabetic rats' hyperglycemia, weight loss, oxidative indicators, and superoxide dismutase activity. It additionally enhanced retinal NF-κB activity and avoided retinal layer disarrangement [111].

Diabetes research encompasses microvascular problems such as diabetic retinopathy (DR), because can be impacted by imbalances in pro- and anti-angiogenesis factors. The proposed retinal pigment epithelium (RPE) is responsible for preserving vision and secreting growth factors as well as protective chemicals. Resveratrol, a natural chemical, can alter neurotrophic factors in the retina, which include pigment epithelium-derived factor (PEDF) and thrombospondin-1. Resveratrol reduces VEGF expression among human adult RPE cells, which slows the progression of proliferative vitreoretinopathy. However, its limited bioavailability restricts its possible use. Several medication delivery techniques are being

evaluated to enhance tissue concentrations. Investigating these pathways may provide new targets for lowering diabetes complications [112].

A research investigation discovered that resveratrol administration reduced retinal inflammation and protected diabetic rats and high-glucose-stimulated retinal endothelial cells (RRECs). PON1 controls inflammatory responses with microvascular problems in DR. Resveratrol also decreased retinal damage for HG-stimulated RRECs. The data imply that resveratrol-induced PON1 might be a potential treatment method to prevent diabetes-related retinopathy (Figure 6) [113].

The work shows how Resveratrol, a naturally occurring polyphenol, may be used to make gold nanoparticles (AuNPs) for the treatment of streptozotocin-induced diabetes in rats. The spherical nanoparticles were tested on diabetic rats to see whether they had any beneficial effects. The study found that AuNPs reduced blood-retinal barrier permeability, enhanced retinal factor expression, and lowered NF-κB p65 and ERK 1/2 phosphorylation. AuNPs may assist in restoring equilibrium between inhibitors and stimulators of angiogenesis, suppress ERK1/2 signaling pathways, and reduce retinal inflammation [114].

Resveratrol, a form of antioxidant, has been demonstrated to improve insulin resistance, oxidative stress, and pro-inflammatory cytokines in type II diabetic patients. The study identified nine probable pathways for resveratrol's impact in DR. Resveratrol has been reported in vitro and in vivo to prevent insult-induced apoptosis associated with retinal cells, presumably through microRNA-29b (miR-29b) inhibition and oxidative stress reduction [116]. Resveratrol increases retinal superoxide dismutase activity. Activating the AMPK/Sirt1/PGC-1α pathway may redu

glucose levels [117]. Resveratrol may reduce inflammation by reducing pro-inflammatory mediators and inhibiting diabetes-induced NF-κB signalling. However, there is conflicting evidence that resveratrol inhibits neovascularization [118]. Due to the scarcity of research and the limitations of animal studies, resveratrol is a promising option for clinical trials treating diabetic retinopathy [119].

4. Catechin

Catechins are important functional components of tea that provide several health advantages, including diabetic relief. Glucose is required to preserve life [120]. Hyperglycemia occurs when the concentration of glucose within the serum surpasses the threshold. Hyperglycemia is mostly caused by low insulin secretion through insulin resistance [121]. Persistent hyperglycemia can result in a variety of conditions, involving retinopathy, nephropathy, neurodegenerative illnesses, and cardiovascular disease, in addition to diabetes [122].

Green tea (catechin) has become a highly popular beverage across the world, and regular consumption has been demonstrated to contribute to health advantages such as chemopreventive effectiveness [123]. More than 795 published research studies have examined the effects of green tea on cancer, with the majority focusing on its chemopreventive properties [124]. It is well accepted that the primary chemopreventive actions of green tea towards cancer are controlled by its polyphenols, which are called catechins. Catechin can prevent experimental diabetic mellitus-induced vascular endothelial alterations in structure and operation [125].

Catechin is a flavonoid found in several types of tea, fruit, chocolate, and wine. Flavan-3-ol is a natural phenol with antioxidant. It is classified as flavan-3-ols (or simply flavanols) and is a member of the flavonoid chemical fam-

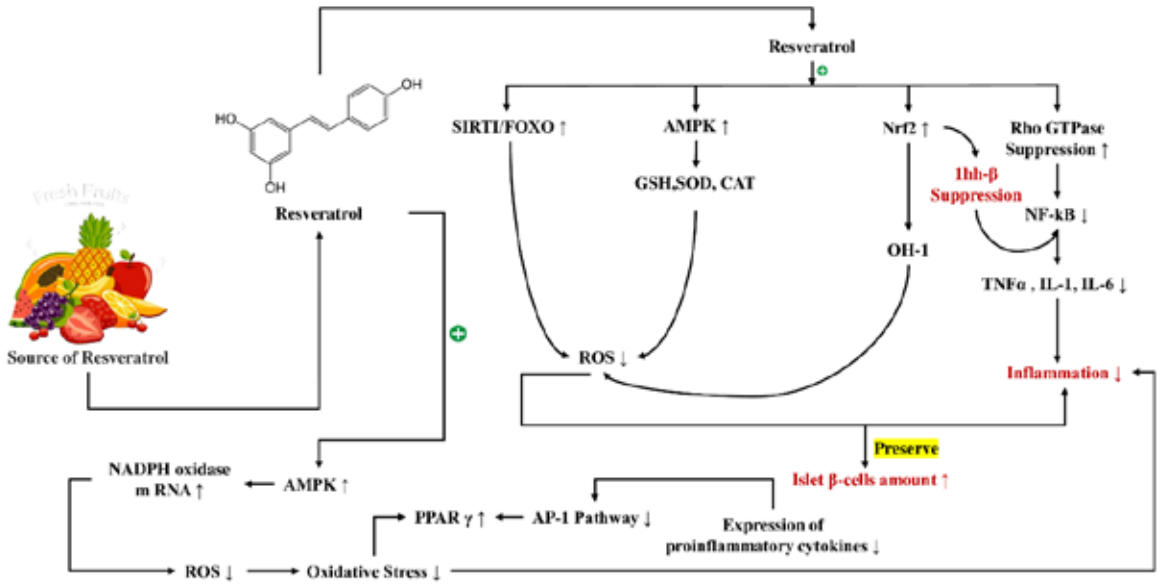


Figure 6. Resveratrol's therapeutic actions in diabetic retinopathy involve reducing oxidative stress, regulating inflammatory pathways, and increasing retinal function, which may reduce retinal damage and consequences [115].

ily [126]. Additionally, it has a substantial antioxidative impact, with antioxidant activity 20 times more powerful than vitamin E as well as six times higher when compared with superoxide dismutase.

Catechin's antioxidant property possesses a detailed effect that can generate antioxidant activity by removing or limiting free radical sequestration between metals, as well as lowering ion oxidation catalysis [127]. Catechins have potential therapeutic effects, including inhibiting α-glucosidase, interacting with glucose transporters, reducing hepatic glucose production, improving pancreatic function, and protecting pancreatic β-cells by inhibiting NF-κB activation [128]. Diabetes is linked to the development of vascular endothelial dysfunction (VED), which can be prevented by catechin hydrate therapy [129].

Evidence from experiments and mechanisms of action

This study examines how catechin affects the expression of HSP27, NF-κB, and inflammatory markers in rats with streptozotocin-induced diabetic retinopathy (DR). The rats were separated into five groups and given varied doses of catechin throughout eight weeks. In STZ-induced DR rats, HSP27 levels rose, whereas IL-1β, IL-6, and TNF-α levels were elevated. Catechin therapy reduced these alterations and decreased NF-κB activation. There was a negative connection between catechin concentrations and inflammatory factor expression. catechin's influence on DR, including its molecular processes, utilizing a DR model and varied catechin concentrations in animals, identifying its effects affecting retinal tissues along with proteins (Figure 7) [130].

5. Rutin

Rutin, a flavonoid, has several major advantages, including antioxidant, anti-diabetic, anticancer, anti-inflammatory, neuroprotective, and cardiovascular properties [132]. Thus, rutin contributes to the preservation of cells' functional as well as structural integrity by reducing oxidative stress.

Rutin also reduces the production of sorbitol, reactive oxygen species, advanced glycation end-product precursors, including pro-inflammatory cytokines [133]. These actions are thought to be responsible for rutin's preventive benefit against hyperglycemia including dyslipidemia-induced nephropathy, retinopathy, neuropathy, liver damage, especially cardiovascular disease [134].

Evidence from experiments and mechanisms of action

This study looks at the neuroprotective effects of flavonoid rutin upon diabetic rat retinas. Hyperglycemia is a neurodegenerative disease because oxidative stress plays a significant role in retinal degeneration. The researchers discovered that rutin had anti-diabetic properties, lowering blood glucose levels while boosting insulin. It also lowered the amounts of neurotrophic factors, apoptotic indicators, and thiobarbituric acid-reactive compounds. This implies that rutin may be a viable flavonoid to reduce retinal damage, including diabetic retinopathy [135].

A study looked at the effect of utilizing gold nanoparticles phytoreduced containing Rutin (AuNPsR) as a possible remedy. The researchers discovered that Rutin increased retinal arteriolar width, decreased inflammation and oxidation, and conserved lens structure. Insulin improved retinal arteriolar diameter despite increased MDA. AuNPsR produced the best results, enhancing fundus appearance, lowering MDA levels, and boosting antioxidant activity. Given the systemic nature of diabetes and Rutin's multiorgan activity, oral administration was recommended, along with a nanotechnology-based formulation, to solve delivery and bioavailability difficulties [136].

Rutin, a medication, has been shown to reduce superoxide generation in response to oxidative stress in human Type II Diabetic Retinopathy cell lines. The study discovered lower levels of caspase-3, higher levels of BDNF, and lower levels of TBARS among Type II Diabetic Melli-

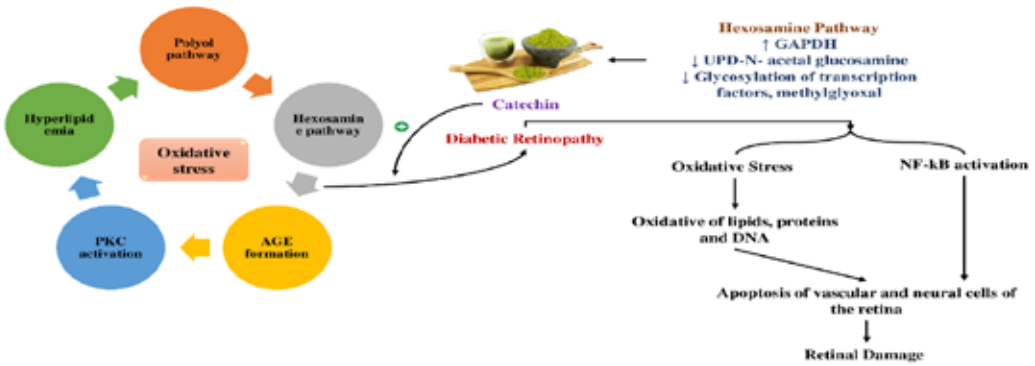


Figure 7. Catechins have been demonstrated in experimental research to reduce retinal inflammation, increase vascular health, and retain retinal integrity, making them a promising treatment agent for diabetic retinopathy [131].

tus and Type II Diabetic Retinopathy samples. Further in vivo research can study the pharmacological effect of rutin on regulating DR [137].

The study shows that dietary flavonoids, such as rutin, can reduce advanced glycation end products (AGE) and so prevent or halt diabetes consequences. Using goat ocular lens proteins as models, rutin reduced glycation in vitro by scavenging free radicals in addition to chelating metal ions. This indicates that rutin may prevent or decrease protein glycation, potentially reducing AGE-mediated diabetes pathogenic states in vivo (Figure 8) [138].

Figure 8. Rutin's preventative advantages in diabetic retinopathy include reduced oxidative stress, inhibition of inflammation, and improved retinal vascular function, indicating that it might be used as a therapy [139].

Rutin efficiently decreases the elevated amounts of thiobarbituric acid-reactive compounds and hydroperoxides seen in diabetes [140]. Rutin was also reported to inhibit microglial activation, including pro-inflammatory cytokines [141]. Despite rutin's numerous positive properties, no research to our knowledge have described the effect of rutin supplementation upon antioxidant, antiapoptotic, and neurotrophic stimulation within the diabetic retina (Table. 2) [142].

Clinical Studies

Additionally, there have only been a few clinical trials looking at the potential benefit of nutraceuticals in the management of DR, and the majority of them have focused on carotenoids [162]. Randomized clinical studies in NPDR patients have revealed that lutein supplementation for three or nine months improves visual acuity as well as contrast sensitivity while decreasing foveal thickness, suggesting that macular oedema is reduced [163].

A placebo-controlled randomized clinical trial alongside people suffering from diabetic maculopathy refractory to conventional therapy yielded similar results, with management of 15 mg crocin tablets every day for three months resulting in a significant improvement in terms of best-corrected visual acuity and central macular thickness [164]. Type 2 diabetes patients with a greater ratio of blood non-pro-vitamin carotenoids (lutein, zeaxanthin, lycopene) to pro-vitamin A carotenoids (α-carotene, β-carotene, and β-cryptoxanthin) had a 66% lower risk for DR (Table 3) [165].

Furthermore, the optical density associated with macular pigment, which contains the carotenoids lutein and zeaxanthin, be lower among individuals with Type 2 diabetes compared with age-matched controls, and even lower in patients with Type 2 diabetes combined with DR [166]. Finally, a retrospective investigation of Type 2 diabetes patients following two years of carotenoid administration found that carotenoids may improve diabetic macular function.

In addition to clinical trials on carotenoids, a few articles have documented the use of various nutraceuticals in individuals experiencing DR [167]. For example, a standardized phytosomal curcuminoid combination (Meriva®) significantly enhances curcumin absorption, and in one study, 38 diabetic patients treated with Meriva® demonstrated improvements in diabetic microangiopathy, including retinopathy, four weeks after treatment.

Furthermore, a recent study examined the potential benefits of green tea [168]. Indeed, a clinic-based, case-con-

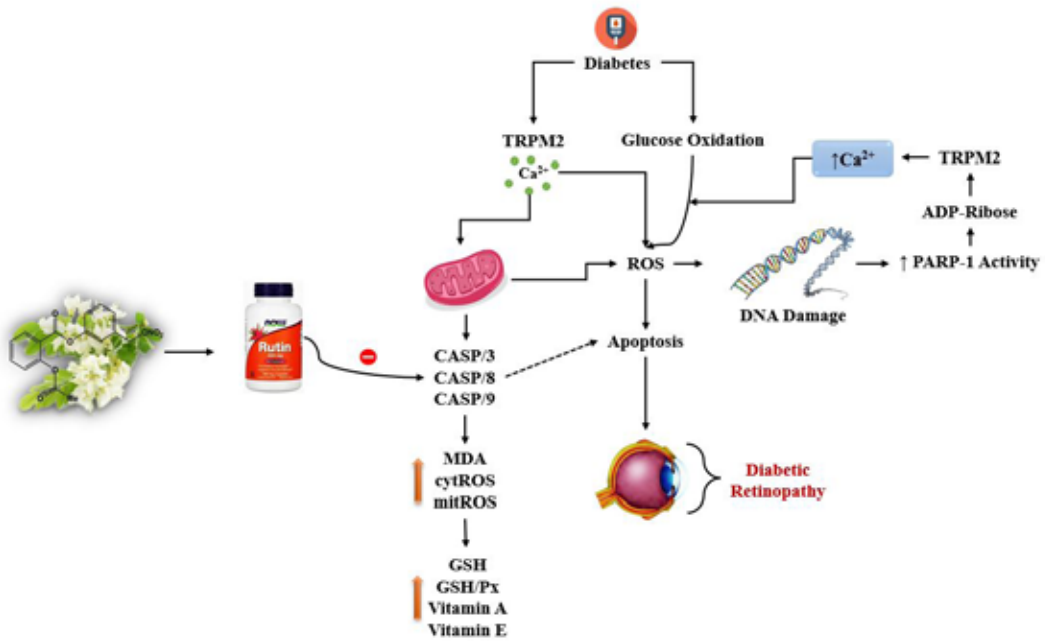
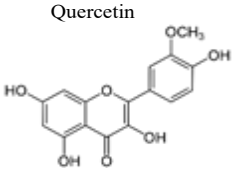
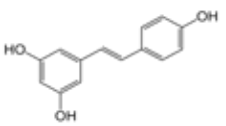
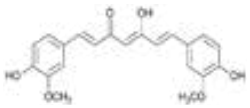
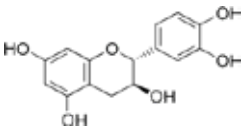
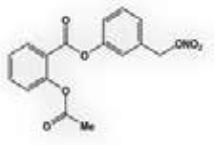


Figure 8. Rutin's preventative advantages in diabetic retinopathy include reduced oxidative stress, inhibition of inflammation, and improved retinal vascular function, indicating that it might be used as a therapy [139].

Table 2. Mechanistic Insights and Marketed Formulations of Key Nutraceuticals in the Prevention and Management of Diabetic Retinopathy

Sr no.	Origin	Compounds and structures	Dose	Animal model and cell line	Key discovery	References
1.	Fruit and veggies (red wine, apples, green tea, onion)	Quercetin 	150 mg/kg for 20 weeks.	STZ-induced diabetic rats	Decreased levels of VEGF and MMP-9. Decreased VEGF RNA as well as protein concentrations	[143]
	Onions, red wine, apples, tea made from green tea, ginkgo biloba, and strawberries.	Quercetin	25 and 50 mg/kg, for 24 weeks	STZ-stimulated diabetes model	Reduced IL-1β, TNF-α, caspase-3, NF-κB, aquaporin-4, increased GFAP levels. Increased GSH levels, CAT, and SOD activity	[144]
	Quercus iberica, Dysosma veitchii, Hypericum ascyron, as well as *Apocynum lancifolium*	Quercetin	10, 20, 30, 40, then 50 μM for 1 day.	ARPE-19 cells were treated using high glucose	Decreased expression of Bax, p53, and cleaved caspase-3. Reduced apoptosis, IL-6, MCP-1, and ROS production. Reduced the NF-κB pathway. Stimulated the PTEN/AKT pathway Increased gene expression of Bcl-2, CDK4, CyclinD1, and MiR-29b.	[145]
	Vegetarian and fruit products (red wine, fruit such as apples, green tea, onions)	Quercetin	20, 40, 80 μmol/L	HRECs are exposed to high glucose levels.	Reduced expression of caspase-1, IL-18, Beclin-1, and NLRP3 decreased angiogenesis along with autophagy	[146]
	Veggies and fruit (red wine, apples, guava, and onions)	Quercetin	150 mg/kg during 16 days.	STZ-induced diabetes in rats	Increased TNF-α, IL6, IL-18, and IL-1β expressions, as well as increased NLRP3 inflammasome activity. Suppressed upregulation of soluble ICAM-1, VEGF, NF-κBp65, and TLR4. Increased ganglion cell count and thickness of the retinal cell layer.	[147]
2.	*Curcuma longa*	Curcumin	10 μM	High glucose induced HRECs	Decreased HREC proliferation, regulated intracellular ROS generation, the expression of VEGF, and release	[148]
	Turmeric (*Curcuma longa*)	Curcumin	15 μM	ARPE19 cells are exposed to H2O2.	Upregulation of oxidative stress	[149]
	Turmeric (*Curcuma longa*)	Curcumin	0.5 μM, 5 μM	Acrolein-induced ARPE-19 cells	Established the PI3/Akt pathway. Enhanced Nrf2 activity as well as other antioxidants.	[150]
	Curcuma longa	Curcumin	25 μM, 6 h	ARPE-19 cells were treated using high glucose	Reduced ROS generation and restored DNMT functioning. Prevented changes to DNA methyltransferase function.	[151]
	Curcuma longa	Curcumin	80 mg/kg each day.	STZ-induced diabetic rats	Prevented the reduction of GSH levels and inhibited oxidative stress.	[152]
	Curcuma longa	Curcumin	Both 100 and 200 mg/kg during 16 weeks.	Diabetic rat model	Decreased diabetes-induced retinal ultrastructure alterations, which include retinal ganglion cell death, retinal thinning, along with photoreceptor cell membranous disc disruption. Downregulated VEGF expression shows antioxidant as well as hypoglycemic properties.	[153]

3.	Grapes, berries, even peanuts.	Resveratrol 	5 mg/kg/day for 4 months.	STZ-nicotinamide induced diabetic retinopathy.	Decreased superoxide dismutase function and oxidative stress repressed lipid peroxidation.	[154]
	Grapes, berries, and peanuts.	Resveratrol	Take 5, 10, and 50 µg/kg/day throughout 12 weeks.	STZ-induced diabetic rats	Reduced retinal vascular permeability as well as inflammatory mediators, especially Ox-LDL, LDL, MCP-1, AGEs, IL-1β, IL-6, IFNγ, as well as VEGF. Reduced Ox-LDL expression along with caspase3 activity.	[155]
	Red wine with grape peel	Resveratrol 	Take 5, 50, 100, even 200 mg/kg over 5 days.	Male C57/B6 mice	Reduced NF-κB nuclear translocation into retinas. Decreased protein concentrations of ICAM-1 as well as MCP-1 in retinal cells	[156]
	Red wine with grape peel	Resveratrol	50 mg/kg for seven days.	STZ-induced diabetes in rats	AMPK activation accelerated NF-κB inhibition and reversed SIRT1 inactivation.	[157]
	Red wine with grape peel	Resveratrol 	20 mg/kg for 4 weeks.	STZ-induced diabetic rats	Downregulated NF-κB via blocking retinal CAMKII activity.	[158]
4.	Green tea	Catechin 	50, 100, and 200 mg/kg for 8 weeks.	Diabetic rats treated with STZ.	NF-κB pathway inhibition leads to decreased levels of IL-1β, IL-6, and TNF-α. Increased HSP27 concentrations	[159]
5.	Onions, apples, tea, with red wine	Rutin	100 mg/kg for 5 weeks.	STZ-induced diabetic rats	Reduced TBARs, caspase-3, along with blood glucose levels. Elevated Bcl-2, GSH, NGF, BDNF, as well as blood insulin levels	[160]
			50 mg/kg for 24 weeks.	STZ-induced diabetic rats	Reduced levels of TNF-α, VEGF, and aldose reductase. Improved fluorescein vascular leakage Increased antioxidant capability	[161]

trol study of diabetic individuals with Type 2 diabetes found that those who drank Chinese green tea every week during at least one year had a 50% lower chance of developing DR compared to those who did not. [169].

Phytochemicals have been demonstrated to protect against diabetic retinopathy (DR), but just a few clinical investigations have looked into their ability to prevent diabetes associated DR [172]. A clinical investigation discovered that taking myricetin with quercetin flavonoids for one year significantly lowered the risk of diabetes [173]. A meta-analysis of randomized controlled trials indicated that green tea catechins reduced fasting blood sugar levels but had no effect on glycated hemoglobin (HbA1c) or fasting blood insulin.

Another research discovered that flavonoids retained retinal sensitivity but did not substantially affect blood pressure, HbA1c levels, central retinal thickness, visual acuity, or microalbuminuria [174]. According to one study, drinking green tea on a daily basis cuts the risk of DR by 50%. A multi-center field research found that Pycnogenol® medication prevented visual loss in diabetic individuals with DR [175].

Possible future directions

Overall, substantial data have shown that nutraceuticals have a good potential for controlling DR, whether by consumption, injections, or topical treatment [176]. Meanwhile, scientists are encouraged to investigate the underlying processes of nutraceuticals using DR-related models [177]. Indeed, the majority of nutraceuticals have potent antioxidant and anti-inflammatory activities. Additionally, several of them have the potential to preserve neurones, neuroglia, and overall epithelial cells while also improving

Table 3. Nutraceutical effects on DR (clinical research).

Sr no.	Dietary Compound	Family of Compound	Type	Dosage	Supplementation Period	Candidates	Effects	Ref.
1.	Omega-3 polyunsaturated fats (DHA/EPA)	Oil	Prospective	1 g/day (460 mg EPA + 380 mg DHA)	6.5 years	T1DM and T2DM (± DR)	× No benefit for DR	[170]
2.	DHA	Oil	Prospective	1050 mg/day	2 years	NPDR (all stages)	× No impact on NPDR progression	[170]
3.	Brudyretina is a high-DHA (1050 mg/d) nutraceutical formulation that contains DHA, EPA, a combination of B vitamins, vitamins C among E, lutein, zeaxanthin, and minerals.	Oil plus others	Prospective	3 × 1.5 g capsules/day	90 days	T2DM with NPDR (n=24)	✓ ↑ Antioxidant capacity, ↓ IL-6; □ No change in BCVA or CMT	[170]
4.	Lutein	Carotenoids	Prospective	10 mg/day	36 weeks	T2DM without NPDR (n=30)	✓ Improved contrast sensitivity	[170]
5.	Lutein (L), as well as zeaxanthin (Z)	Carotenoids	Retrospective	Z (0.5 mg/day) + L (6 mg/day)	4 months	NPDR (n=72)	× No significant benefit	[170]
6.	Lycopene	Carotenoids	Cross-sectional	Dietary intake via FFQ	-	T2DM and healthy controls	✓ Reduced oxidative stress	[170]
7.	Anthocyanin	Polyphenol	Prospective	320 mg/day	4 weeks	Healthy, T2DM, T2DM-at-risk	✓ ↓ IL-6, IL-18, TNF-α (Anti-inflammatory)	[170]
8.	Curcumin, artemisia, bromelain as well as black pepper	Combo	Prospective	Cur (200 mg), Art (80 mg), Brom (80 mg), BP (2 mg)	6 months	T2DM (± mild–moderate DME)	✓ ↑ Visual acuity, ↓ CMT, ↑ Vessel density	[171]

retinal and vascular function. Nutraceuticals may have a role in DR by influencing pathways such as NF-κB and HIF-1α signalling [178].

Polyphenols provide an efficient and secure substitute to standard treatments for diabetic retinopathy. Phytochemicals have been proven in studies to change BRB disruption, enhance oxidative status, and reduce proinflammatory mediator announcement, restoring retina thickness while inhibiting neurodegeneration as well as apoptosis [179]. Despite fewer trials, polyphenols can be delivered through supplements and food to diabetic individuals, lowering the prevalence of diabetes and the development of diabetic retinopathy [180].

However, further clinical trials are required to confirm the usage and importance of polyphenols in treating diabetic retinopathy. Furthermore, the limited bioavailability attributes of polyphenolic substances and the lack of suitable delivery techniques impede their development [181].

Conclusion

The worldwide nutraceutical industry is expected to reach USD 488.41 billion by 2024, with an average yearly growth rate of 5.09% from 2024 through 2029. Nutraceuticals have shown promise in treating diabetic retinal disease (DR) by oral, injectable, and topical treatment.

They contain high antioxidant and anti-inflammatory capabilities, which may protect neurones, neuroglia, and epithelial cells while increasing retinal function. However, their actual therapeutic application is restricted due to poor bioavailability and compromised hepatic and kidney health in some individuals.

Additional study is required to support as well as promote their therapeutic use in DR. Nutraceuticals can help with diabetic retinal degeneration (DR) by reducing inflammation, oxidative stress, neurodegeneration, and especially vascular lesions. However, there is inadequate data to support their use in therapeutic therapy. More study is required to discover the optimal mix of nutraceuticals, dose, and duration for therapeutic effects.

Conflict of Interests

The authors declare no conflict of interest.

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