Diabetic Retinopathy

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Background

Diabetic retinopathy (DR) is a neurovascular complication of type 1 and type 2 diabetes (T1D and T2D) caused by deterioration of the blood-retinal barrier, which limits movement of fluid, molecules, and cells between blood vessels and retinal tissue.[1] This breakdown of the blood-retinal barrier is instigated by the following metabolic responses to elevated blood glucose levels[2,3]:

- increased sorbitol production through the polyol glucose metabolism pathway
- increased advanced glycation end-product (AGE)/receptor interactions
- increased hexosamine pathway products
- increased protein kinase C (PKC) activity
- increased polyADP-ribose polymerase (PARP) activation
- increased tissue renin-angiotensin system activation

These changes in metabolic function exacerbate production of reactive oxygen and nitrogen species (ROS and RNS), overwhelming natural antioxidant defenses and tipping the reduction-oxidation balance in favor of oxidation. The retina is especially vulnerable to oxidative stress due to chronic light exposure, high utilization of oxygen, and high concentration of polyunsaturated fatty acids.[4] Increased production of ROS and RNS damages cellular DNA, proteins, carbohydrates, and lipids, and induces inflammatory signaling.[2,5] This leads to vascular, neural, and retinal cell damage; breakdown of the blood-retinal barrier; and, proliferation of blood vessels and retinal scarring.[2] Unfortunately, high oxidative and nitrosative stress further aggravate the metabolic dysfunction described above, resulting in a perpetual cycle of tissue damage.[3]

In addition, epigenetic and micro-RNA alterations leading to dysregulated protein synthesis appear to induce epigenetic alterations, resulting in the formation of “metabolic memory” in retinal cells that may play a key role in the development of DR.[2]

Stages

DR is classified as non-proliferative or advanced proliferative retinopathy. The non-proliferative stage is characterized by increased blood vessel permeability and capillary blockages. Micro-aneurysms, micro-hemorrhages, and lipid deposits called hard exudates may be visualized through fundus photography but may not affect vision at this stage.[6] The proliferative stage is characterized by new and dysfunctional blood vessel growth, stimulated in part by low oxygen concentrations and dysfunctional growth factor signaling.[7] The proliferation of fragile blood vessels can lead to vitreous hemorrhage or retinal detachment, complications that cause severe vision loss. Diabetic macular edema (fluid accumulation in and around the macula of the retina

due to breakdown of the blood-retinal barrier) can occur at either stage of DR and can also impair vision.[6,7]

Correlations and Risk Factors

The major risk factors for DR are high HgbA1c, longstanding diabetes, and hypertension.[1] In addition, a meta-analysis revealed a strong relationship between obstructive sleep apnea and DR risk in T1D and T2D.[8] Although only one study in the meta-analysis was performed in T1D subjects, the results from that study were especially robust, noting a 4.5-fold increase in DR risk in those with sleep apnea compared to those without. Interestingly, the study found no correlations between sleep apnea and body mass index, HgbA1c values, or scores on sleepiness scales, highlighting the potential importance of sleep apnea screening for people with T1D.[9]

In large clinical trials, intensive blood glucose control, achieving average HgbA1c values of 7.0-7.2%, has been shown to prevent onset and progression of DR in patients with both T1D and T2D compared to less intensive blood glucose management.[10,11] The benefits of aggressive blood pressure lowering are less evident and more controversial; however, standard recommendations for a blood pressure management target of 140/80 appear to be supportable.[1,12] In addition, despite conflicting evidence linking high cholesterol and triglyceride measurements with DR, there is emerging evidence that low apolipoprotein A1, high apolipoprotein B, and high apolipoprotein B/A1 ratio may be independently correlated with DR.[10,13] Furthermore, high homocysteine levels have been shown to be a risk predictor for DR in those with T2D, but not T1D.[14]

Although blood glucose control remains the most closely associated risk factor for DR, HgbA1c may only account for up to 11% of DR risk, suggesting other factors still under investigation, such as heritability and epigenetics, may have a substantial role in predicting risk.[1] Another issue deserving attention is that of glucose variability. Data from studies using continuous glucose monitoring devices indicate a high degree of glucose variability, even in cases in which HgbA1c values indicate overall good blood glucose control, may contribute to DR risk in cases of T1D and T2D.[15-17]

The coincidence of rapid improvement in glucose control and onset or marked worsening of DR is a phenomenon called “early worsening.” Early worsening was first described in the 1980s, yet the underlying mechanism remains a mystery. Despite its alarming nature, early worsening does not seem to negate the long-term benefits of intensive hypoglycemic therapy on DR progression.[18,19]

Conventional Treatments

Laser photocoagulation is considered the gold standard treatment for proliferative DR and is highly effective for treating macular edema, but because it can also damage retinal cells and thereby contribute to vision loss, it is generally used as a supportive or rescue therapy along with other medical approaches.[6]

Anti-angiogenic agents, especially **vascular endothelial growth factor (VEGF)-inhibitors**, and **corticosteroids** are the most widely used conventional therapies for DR.[6] In most cases, these medications are administered via injections into the vitreous humor; however, the effects are short-lived, and intravitreal injections have inherent risks.[6] Sustained delivery technologies are being developed to mitigate the risks, costs, and inconvenience associated with multiple injections.[7]

Calcium dobesilate is a pharmacologic antioxidant that has been used to treat DR and other microvascular disorders since the 1960s.[20] In animal models of diabetes, calcium dobesilate reduced inflammatory and free radical retinal neurovascular injury and prevented hyperglycemia-induced alterations in gene expression.[21,22] It may also inhibit angiogenesis.[23]

In clinical research, a dose of 500 mg daily for three months was also found to improve endothelial function and reduce C-reactive protein levels in patients with severe non-proliferative or proliferative DR.[24] A placebo-controlled trial in 194 T2D patients with early DR showed treatment with 2 grams calcium dobesilate daily for two years slowed deterioration of the blood-retina barrier and progression of DR.[25] Similarly, 2 grams per day of calcium dobesilate stabilized the blood-retina barrier in 41 subjects with T2D and DR in a one-year placebo-controlled trial.[26] Calcium dobesilate has also been shown to improve blood viscosity and capillary fragility in people with DR.[27,28] However, five years of treatment with 1,500 mg per day calcium dobesilate did not reduce incidence of macular edema in T2D patients with mild to moderate nonproliferative DR in a placebo-controlled trial.[29]

Other pharmacotherapy approaches currently in use or under investigation fall into the following general categories[3,6,7]:

- non-steroidal anti-inflammatory topical and intravitreal drugs
- hypoglycemic agents such as metformin and insulin
- antihypertensive medications including angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)
- hypolipidemic agents such as statins and fibrates
- PKC and PARP inhibitors
- vitreous agents

Pluripotent stem cell therapy is an emerging area of investigation. Mesenchymal stem cells can absorb free radicals, and may stimulate neurovascular repair. So far, research into the potential benefits of stem cell therapies for DR are limited to in vitro studies.[30]

Natural Therapies

Proanthocyanidins

Both grape seed and pine bark proanthocyanidins have been studied for their potential benefits in DR. One trial compared grape seed proanthocyanidin extract (50 mg three times daily) to calcium dobesilate (250 mg three times daily) or placebo in 124 participants with T2D and non-proliferative DR with retinal thickening and hard exudates. After 12 months, grape seed extract was more effective than calcium dobesilate and placebo at reducing the severity of hard exudates

by at least two categories: 43.9% of those receiving grape seed extract had this degree of improvement, compared to 14.29% of those receiving calcium dobesilate and 8% of those receiving placebo. Those using grape seed extract also had greater diminishment in retinal volume and thickness than the other participants, however only the volume change was statistically significant.[31] Research in animals further suggests grape seed extract may reduce AGE formation, angiogenesis, and hyperglycemia-induced changes in protein expression, and protect against hyperglycemia-related free radical-induced vascular and retinal injury.[32,33]

A proanthocyanidin-rich extract from pine bark called pycnogenol has also demonstrated benefits in treating DR. A 2001 review of five previous clinical trials with a combined total of 1,289 participants concluded pycnogenol can safely and effectively help slow progression of, or reverse, DR.[34] In a placebo-controlled trial including 68 subjects with T2D and non-proliferative DR, taking 50 mg pycnogenol, along with 30 mg of vitamin E and 20 mg of coenzyme Q10, daily for six months led to reductions in free radical levels and retinal thickness.[35] Another placebo-controlled trial included 46 participants with T2D and early-stage DR, marked by mild to moderate macular edema and no retinal exudates or hemorrhages. Those given 150 mg pycnogenol per day for two months experienced improvements in macular edema, retinal blood flow and thickness, and vision.[36]

Alpha-Lipoic Acid

Alpha-lipoic acid is an important nutrient for mitochondrial function. It has antioxidant properties and can act as a reducer of oxidized forms of vitamins C and E. Because of its insulin-mimicking activity and capacity to restore reduction-oxidation balance, its use in treating diabetes and diabetes complications has been widely investigated.[37,38]

In one clinical trial, 12 participants with T1D, 48 participants with T2D, and 20 healthy controls were randomly assigned to receive 300 mg lipoic acid per day or placebo for 3 months. Among the participants with diabetes, some in each group (T1D and T2D) had non-proliferative DR and the rest did not have DR. Those who received alpha-lipoic acid experienced stable or increased contrast sensitivity (a highly sensitive test to detect visual impairment), while those receiving placebo experienced reductions in contrast sensitivity.[39] Another trial included 32 participants with well-controlled pre-retinopathic diabetes. After receiving 400 mg alpha-lipoic acid per day (along with genistein and vitamins not otherwise described) or placebo for 30 days, alpha-lipoic acid use was associated with higher antioxidant status and improvement of retinal function as assessed by electroretinogram.[40] However, in a 2-year, randomized, placebo-controlled trial with 267 participants with T2D, those assigned to take 600 mg of alpha-lipoic acid per day did not have a lower occurrence of macular edema than those assigned to placebo, and visual acuity did not change in either group, making it impossible to detect any effect of alpha-lipoic acid on retinal health.[41]

Findings from research using animal models of T1D suggest alpha-lipoic acid can protect against DR by reducing oxidative and nitrosative damage to retinal cells and preserving microvascular health.[42-47] In vitro and animal studies have found alpha-lipoic acid may inhibit expression of VEGF.[46,48] Alpha-lipoic acid may even be able to help reverse metabolic memory resulting from long-term hyperglycemia, according to results from on study in rats.[49]

Alpha-lipoic acid has been shown to be effective in treatment of other diabetes complications. Reports from clinical trials show alpha-lipoic acid supplementation can help reduce symptoms of diabetic neuropathy in those with T1D and T2D.[50,51] In particular, 600 mg of lipoic acid per day appears to reverse some symptoms of neuropathy in diabetes patients.[52-54]

The local use of alpha-lipoic acid in the form of eye drops may have better long term safety, given concerns about possible pro-oxidant effects with long term systemic use. One study reported that a nanomicellized alpha-lipoic acid eye drop had better solubility and retention in corneal tissue compared to other eye drop preparations.[55]

Carotenoids

The carotenoids lutein and zeaxanthin (plant pigments), along with meso-zeaxanthin (a metabolite of lutein), are naturally deposited in the retina, and are especially concentrated in the macula, where they participate in visual function and act as the primary defense against oxidative and nitrosative damage.[4,56] Experimental models of diabetes show lutein and zeaxanthin protect retinal cells by reducing oxidative stress, inhibiting oxidative retinal damage, and suppressing pro-angiogenic signaling.[4,57]

A randomized controlled trial was conducted in 31 subjects with T2D and mild to moderate non-proliferative DR. They received either 10 mg lutein per day or placebo for 36 weeks. At the end of the trial, visual acuity was slightly improved in the lutein group, and the effect was more pronounced in those with greater visual impairment at baseline. In addition, slight improvements in contrast and glare sensitivity were noted. None of these observations reached statistical significance in this small cohort.[58] In another placebo-controlled trial that included 60 participants with T1D or T2D with non-proliferative DR and macular edema, taking a supplement containing 6 mg lutein and 0.5 mg zeaxanthin daily for three months was associated with improvements in visual acuity, contrast sensitivity, and macular edema.[59] In a two-year pilot trial, 60 participants with T2D taking a daily supplement providing 10 mg lutein, 2 mg zeaxanthin, and 10 mg meso-zeaxanthin had improved measures of retinal health and preserved visual acuity.[60]

Crocin and crocetin are carotenoids found in saffron and exhibit strong antioxidant and anti-inflammatory properties.[61] Both crocin and crocetin have been shown to protect retinal cells from the damaging effects of free radicals and ischemia.[62,63] A placebo-controlled trial included 60 participants with DR that had progressed despite conventional interventions and assigned them to receive either 5 mg or 15 mg of crocin or placebo daily for three months. At the end of the trial, those taking 15 mg crocin per day had significant improvements in visual acuity and retinal thickness compared to placebo.[64]

Curcumin

The non-flavonoid polyphenol curcumin has been shown to reduce inflammatory and oxidative damage induced by high glucose conditions in cultured retinal cells.[65-68] It has also been found to enhance expression of antioxidant enzymes and inhibit expression of growth factors such as VEGF, and may thereby help suppress metabolic memory and progression of DR to the proliferative stage.[4,69,70] In animal models of T1D, oral curcumin reduced blood glucose levels, and prevented retinal changes associated with DR by modulating the retinal antioxidant system

and preserving neurovascular health.[71,72] Findings from another animal study suggest attaching curcumin to a hydrophilic carrier may increase accumulation of curcumin in the retina.[73]

A phospholipid-bound form of curcumin (Meriva®) was used in a pilot study that included 12 eyes from 11 subjects with chronic diabetic macular edema. After three months of treatment with 500 mg lecithin-bound curcumin (equivalent to 100 mg curcumin) twice daily, visual acuity was stable in 16% of eyes and improved in 84%, and macular edema was stable in 8% of eyes and reduced in 92%.[74] Another preliminary trial examined the effects of the same dose of lecithin-bound curcumin in 38 subjects with diabetes-related microangiopathy and retinopathy. After four weeks, improvements were noted in peripheral microvascular function, retinal blood flow, macular edema, and visual acuity.[75]

Ginkgo biloba

In clinical research, 140 people with uncomplicated T2D were randomly assigned to receive ginkgo leaf tablets, at a dose of 19.2 mg three times per day, plus a traditional Chinese patent medicine called Liuwei Dihuang, or placebo in addition to standard conventional treatments (anti-hyperglycemics, antihypertensives, anti-hyperlipidemics, etc). Ginkgo plus Liuwei Dihuang treatment was associated with lower risk of DR compared to placebo (8.5% versus 25%) after three years.[76] A pilot trial in 25 T2D patients with DR found ginkgo extract (Egb 761) improved red blood cell membrane integrity and fluidity, hemodynamics, and retinal blood flow after three months.[77] In a placebo-controlled trial in 29 subjects with early DR, those given ginkgo extract for six months had improvement in color vision, while those receiving experienced worsening of their color vision deficits.[78]

Some of the possible mechanisms behind ginkgo's positive effects were identified through research in diabetic rats: after ten days of treatment with ginkgo extract, plus white willow and red berry extracts, measures of oxidative stress, inflammatory activity, and angiogenic signaling via VEGF were reduced.[79]

Traditional Chinese medicine

A traditional Chinese medicine (TCM) approach using herbs that tonify qi and yin and invigorate blood has been used to treat DR. A meta-analysis of ten randomized controlled studies including a total of 661 participants concluded this TCM herbal approach to DR, called Yiqi Yangyin Huoxue, improves vision, retinal structure, retinal capillary health, and blood viscosity and red blood cell fluidity.[80]

B Vitamins

Thiamine (vitamin B1) and its lipid-soluble derivative benfotiamine have demonstrated anti-glycative properties that could make them useful in preventing and treating microvascular damage and DR.[81] Thiamine pyrophosphate is a cofactor for the transketolase enzyme, activation of which prevents accumulation of AGEs, and reduces activation of the polyol, protein kinase C, and hexosamine pathways.[82-84] Both benfotiamine and high-dose thiamine have been found to prevent DR in animal models of diabetes.[85-87] Benfotiamine, due to its lipid-soluble nature, may raise intracellular thiamine levels more efficiently than water-soluble forms of thiamine and have stronger anti-glycative properties.[88,89]

A pilot trial that included 9 participants with T1D found the combination of 300 mg benfotiamine plus 600 mg slow-release alpha-lipoic acid, taken twice daily for 28 days, reduced AGE formation and inhibited the hexosamine pathway; however, treatment also decreased activity of the anti-atherosclerotic enzyme prostacyclin synthase, indicating a possible pro-oxidant effect of alpha-lipoic acid.[90]

Clinical findings regarding the use of benfotiamine to treat other diabetes complications have been mixed. Initial findings in patients with diabetic polyneuropathy suggested benfotiamine, at doses of 320-400 mg per day, improved nerve function and reduced symptoms,[91-93] but a randomized controlled trial that included 67 participants with T1D-associated neuropathy found no benefit from 300 mg of benfotiamine per day after two years of treatment.[94] Another pair of controlled trials in subjects with diabetic nephropathy found 900 mg of benfotiamine per day for 12 weeks did not improve renal function or reduce plasma or urinary AGE levels, improve endothelial function, or reduce systemic inflammation.[95,96]

Pyridoxal (vitamin B6), in the active form pyridoxal 5-phosphate, is also a well described inhibitor of AGE formation.[97] It may also protect against microvascular damage in diabetics through its action as a methyl donor with a key role in homocysteine metabolism, along with vitamins B12 and folate. In a pilot trial, supplementing with a combination of 70 mg pyridoxal-5-phosphate, 6 mg L-methylfolate calcium, and 4 mg methylcobalamin daily for six months led to improvements in seven participants with T2D and mild to moderate non-proliferative DR. Specifically, 12 of 14 eyes of participants completing the study showed reductions in retinal edema and increases in light sensitivity.[98] Only additional research will determine whether this promising observation for those with T2D is relevant in cases of T1D, which do not appear to be correlated with altered homocysteine metabolism.

Tea Catechins

Tea and its catechins have demonstrated beneficial effects against DR in epidemiologic, experimental, and animal studies. An epidemiologic study done in China found diabetic patients who reported consuming one or more cups of green tea weekly for at least one year of their life were less likely to have DR than those who reported no regular green tea drinking.[99]

Treatment with epigallocatechin-gallate (EGCG) has been found to normalize retinal cell function, inhibit VEGF expression, and decrease free radical production and retinal damage in retinal cells cultured in a high-glucose environment.[100-102] One study also found EGCG inhibited retinal pigment epithelial cell proliferation and migration, the upregulation of which is implicated in DR progression to the proliferative stage.[103] Epicatechin has been found to break down AGEs and reduce their accumulation in the retinas of diabetic rats,[104] and suppress angiogenesis and deterioration of the blood-retina barrier in experimental and animal research.[105] In diabetic rats, treatment with intravitreal injections of catechins reduced oxidative stress as well as inflammatory and angiogenic signaling in the retina.[106,107]

Fish Oil

A large observational study found that getting 500 mg per day of long-chain polyunsaturated omega-3 fatty acids was associated with a 48% lower risk of DR in subjects with T2D.[108] In a pilot trial with 48 participants, fish oil supplementation reportedly helped prevent progression in

those with early-stage DR.[109] In animal models of diabetes, docosahexaenoic acid (DHA) reduced inflammatory damage in the blood vessels and retina.[110,111]

Vitamin E

Although vitamin E plays an essential role in preventing lipid peroxidation and preserving neurovascular health, little research into its potential to help prevent onset or progression of DR has been conducted. Clinical research in people with T1D and T2D have shown vitamin E improves retinal blood flow and protects red blood cell membrane fluidity.[112,113]

Anthocyanins

A growing body of evidence support the beneficial effects on anthocyanins on cardiovascular, metabolic, and ocular health.[57,114,115] Epidemiologic studies suggest anthocyanin consumption is associated with protection against diabetes and its complications, and clinical trials show anthocyanins and anthocyanin-rich foods improve blood glucose regulation and insulin sensitivity, as well as reduce inflammation, increase antioxidant capacity, and positively alter gene expression.[114,116] In cultured retinal capillary endothelial cells exposed to high glucose conditions, blueberry anthocyanins prevented cellular injury by reducing oxidative and nitrosative stress, inhibiting inflammatory signaling, and decreasing VEGF expression.[117] Similar effects have been seen in diabetic rats.[118,119]

Resveratrol

Resveratrol is a non-flavonoid polyphenol with well described antioxidant and anti-inflammatory activities. Numerous in vitro and animal studies have been performed to evaluate its effects on retinal health in the context of diabetes.[120,121] Findings from these studies suggest resveratrol may benefit the diabetic retina by reducing oxidative stress and free radical damage, decreasing inflammatory signaling, suppressing angiogenesis, and preventing retinal cell ischemia/reperfusion injury and degeneration.[122-128]

Taurine

The non-essential amino acid taurine plays an important role in regulation of glucose metabolism. Taurine levels are lower in diabetics compared to healthy people, and this may contribute to risks of complications, including retinopathy.[129-131] In animal models of diabetes, taurine supplementation reduced expression of VEGF, normalized expression of other proteins associated with retinopathy, and reversed structural changes indicative of DR.[132] Taurine has also been shown to have lasting benefits on retinal health in diabetic animals.[133]

Quercetin

Several studies have found quercetin inhibits neurodegeneration and inflammation-induced angiogenesis in the retinas of diabetic laboratory animals.[134-137]

Combination Therapies

Some studies have examined the effects of combination supplements containing docosahexaenoic acid (DHA), antioxidants, vitamins, and minerals in people with DR. In one such study, a daily supplement providing 1,050 mg docosahexaenoic acid and smaller amounts of other omega-3 fatty acids; 9 mg lutein and 0.9 mg zeaxanthin; 6 mg glutathione, 80 mg vitamin C, and 12 mg vitamin E; and small amounts of B complex vitamins, zinc, copper,

selenium, and magnesium was compared to placebo in 24 T2D patients with non-proliferative DR. After 90 days, only those taking the supplement showed improvements in macular function.[138] In a two-year study with 62 participants suffering from diabetes-related macular edema, the same supplement was found to augment the positive effects of intravitreal ranibizumab (an anti-VEGF immunotherapy agent applied monthly for the first four months of the study) on macular thickness.[139] Another trial evaluated the use of a similar supplement by T2D patients, with and without DR, for 18 months and found those given the supplement had higher total antioxidant activity than matched participants not given the supplement.[140]

Another study included 67 adults with T1D or T2D and mild to moderate DR or no evidence of retinopathy. They were assigned to receive treatment with a combination supplement (containing vitamins C, D3 and E, zinc, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], alpha-lipoic acid, coenzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetyl cysteine, grape seed extract, resveratrol, turmeric root extract, green tea leaf, and pycnogenol) or placebo. After six months, those receiving the supplement had better visual function, but no changes in retinal thickness were observed.[141]

Conclusions

Diabetic retinopathy occurs for many of the same reasons, whether it is a complication of T1D or T2D; namely, dysregulation of glucose metabolism, increased formation of advanced glycation end products, increased oxidative stress, increased inflammatory signaling, increased angiogenesis, and epigenetic alterations. Although most of the research on diabetic retinopathy has been performed in people with T2D, it is likely that natural therapies—even those that have not yet been studied—that prevent or reverse these shared mechanisms have the greatest promise for treating DR in both T1D and T2D. Carotenoids offer the additional advantage of naturally accumulating in the retina. Other promising natural agents have affinity for the vasculature. Only one study examined the adjunctive use of natural therapies to increase the efficacy of conventional treatment. This is an application that warrants more attention.

References:

1. Simo-Servat O, Hernandez C, Simo R. Diabetic Retinopathy in the Context of Patients with Diabetes. *Ophthalmic Res.* 2019:1-7.
2. Mahajan N, Arora P, Sandhir R. Perturbed Biochemical Pathways and Associated Oxidative Stress Lead to Vascular Dysfunctions in Diabetic Retinopathy. *Oxid Med Cell Longev.* 2019;2019:8458472.
3. Whitehead M, Wickremasinghe S, Osborne A, Van Wijngaarden P, Martin KR. Diabetic retinopathy: a complex pathophysiology requiring novel therapeutic strategies. *Expert Opin Biol Ther.* 2018;18(12):1257-1270.

4. Rossino MG, Casini G. Nutraceuticals for the Treatment of Diabetic Retinopathy. *Nutrients.* 2019;11(4).
5. Al-Kharashi AS. Role of oxidative stress, inflammation, hypoxia and angiogenesis in the development of diabetic retinopathy. *Saudi J Ophthalmol.* 2018;32(4):318-323.
6. Wang W, Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. *Int J Mol Sci.* 2018;19(6).
7. Lu L, Jiang Y, Jaganathan R, Hao Y. Current Advances in Pharmacotherapy and Technology for Diabetic Retinopathy: A Systematic Review. *J Ophthalmol.* 2018;2018:1694187.
8. Zhu Z, Zhang F, Liu Y, et al. Relationship of Obstructive Sleep Apnoea with Diabetic Retinopathy: A Meta-Analysis. *Biomed Res Int.* 2017;2017:4737064.
9. Manin G, Pons A, Baltzinger P, et al. Obstructive sleep apnoea in people with Type 1 diabetes: prevalence and association with micro- and macrovascular complications. *Diabet Med.* 2015;32(1):90-96.
10. Hainsworth DP, Bebu I, Aiello LP, et al. Risk Factors for Retinopathy in Type 1 Diabetes: The DCCT/EDIC Study. *Diabetes Care.* 2019;42(5):875-882.
11. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol.* 2017;5(6):431-437.
12. Do DV, Wang X, Vedula SS, et al. Blood pressure control for diabetic retinopathy. *Cochrane Database Syst Rev.* 2015;1:Cd006127.
13. Sasongko MB, Wong TY, Nguyen TT, et al. Serum apolipoproteins are associated with systemic and retinal microvascular function in people with diabetes. *Diabetes.* 2012;61(7):1785-1792.
14. Lei X, Zeng G, Zhang Y, et al. Association between homocysteine level and the risk of diabetic retinopathy: a systematic review and meta-analysis. *Diabetol Metab Syndr.* 2018;10:61.
15. Picconi F, Parravano M, Ylli D, et al. Retinal neurodegeneration in patients with type 1 diabetes mellitus: the role of glycemic variability. *Acta Diabetol.* 2017;54(5):489-497.
16. Zhao Q, Zhou F, Zhang Y, Zhou X, Ying C. Fasting plasma glucose variability levels and risk of adverse outcomes among patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract.* 2019;148:23-31.
17. Rosa L, Zajdenverg L, Souto DL, et al. HbA1c variability and long-term glycemic control are linked to diabetic retinopathy and glomerular filtration rate in patients with type 1 diabetes and multiethnic background. *J Diabetes Complications.* 2019.
18. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. *Diabetes Obes Metab.* 2019;21(3):454-466.
19. Jingi AM, Tankeu AT, Ateba NA, Noubiap JJ. Mechanism of worsening diabetic retinopathy with rapid lowering of blood glucose: the synergistic hypothesis. *BMC Endocr Disord.* 2017;17(1):63.
20. Liu J, Li S, Sun D. Calcium Dobesilate and Micro-vascular diseases. *Life Sci.* 2019;221:348-353.

21. Voabil P, Liberal J, Leal EC, et al. Calcium Dobesilate Is Protective against Inflammation and Oxidative/Nitrosative Stress in the Retina of a Type 1 Diabetic Rat Model. *Ophthalmic Res.* 2017;58(3):150-161.
22. Sola-Adell C, Bogdanov P, Hernandez C, et al. Calcium Dobesilate Prevents Neurodegeneration and Vascular Leakage in Experimental Diabetes. *Curr Eye Res.* 2017;42(9):1273-1286.
23. Cuevas P, Sanchez I, Lozano RM, Gimenez-Gallego G. Dobesilate is an angiogenesis inhibitor. *Eur J Med Res.* 2005;10(9):369-372.
24. Javadzadeh A, Ghorbanihaghjo A, Adl FH, Andalib D, Khojasteh-Jafari H, Ghabili K. Calcium dobesilate reduces endothelin-1 and high-sensitivity C-reactive protein serum levels in patients with diabetic retinopathy. *Mol Vis.* 2013;19:62-68.
25. Ribeiro ML, Seres AI, Carneiro AM, et al. Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomised double-blind study. *Graefes Arch Clin Exp Ophthalmol.* 2006;244(12):1591-1600.
26. Leite EB, Mota MC, de Abreu JR, Cunha-Vaz JG. Effect of calcium dobesilate on the blood-retinal barrier in early diabetic retinopathy. *Int Ophthalmol.* 1990;14(2):81-88.
27. Benarroch IS, Brodsky M, Rubinstein A, Viggiano C, Salama EA. Treatment of blood hyperviscosity with calcium dobesilate in patients with diabetic retinopathy. *Ophthalmic Res.* 1985;17(3):131-138.
28. Vojnikovic B. Doxium (calcium dobesilate) reduces blood hyperviscosity and lowers elevated intraocular pressure in patients with diabetic retinopathy and glaucoma. *Ophthalmic Res.* 1991;23(1):12-20.
29. Haritoglou C, Gerss J, Sauerland C, Kampik A, Ulbig MW. Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2009;373(9672):1364-1371.
30. Ludwig PE, Freeman SC, Janot AC. Novel stem cell and gene therapy in diabetic retinopathy, age related macular degeneration, and retinitis pigmentosa. *Int J Retina Vitreous.* 2019;5:7.
31. Moon SW, Shin YU, Cho H, Bae SH, Kim HK. Effect of grape seed proanthocyanidin extract on hard exudates in patients with non-proliferative diabetic retinopathy. *Medicine (Baltimore).* 2019;98(21):e15515.
32. Sun Y, Xiu C, Liu W, Tao Y, Wang J, Qu YI. Grape seed proanthocyanidin extract protects the retina against early diabetic injury by activating the Nrf2 pathway. *Exp Ther Med.* 2016;11(4):1253-1258.
33. Li M, Ma YB, Gao HQ, et al. A novel approach of proteomics to study the mechanism of action of grape seed proanthocyanidin extracts on diabetic retinopathy in rats. *Chin Med J (Engl).* 2008;121(24):2544-2552.
34. Schonlau F, Rohdewald P. Pycnogenol for diabetic retinopathy. A review. *Int Ophthalmol.* 2001;24(3):161-171.
35. Domanico D, Fragiotta S, Cutini A, Carnevale C, Zompatori L, Vingolo EM. Circulating levels of reactive oxygen species in patients with nonproliferative diabetic retinopathy and the influence of antioxidant supplementation: 6-month follow-up. *Indian J Ophthalmol.* 2015;63(1):9-14.

36. Steigerwalt R, Belcaro G, Cesarone MR, et al. Pycnogenol improves microcirculation, retinal edema, and visual acuity in early diabetic retinopathy. *J Ocul Pharmacol Ther.* 2009;25(6):537-540.
37. Gomes MB, Negrato CA. Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. *Diabetol Metab Syndr.* 2014;6(1):80.
38. Rochette L, Ghibu S, Muresan A, Vergely C. Alpha-lipoic acid: molecular mechanisms and therapeutic potential in diabetes. *Can J Physiol Pharmacol.* 2015;93(12):1021-1027.
39. Gebka A, Serkies-Minuth E, Raczynska D. Effect of the administration of alpha-lipoic acid on contrast sensitivity in patients with type 1 and type 2 diabetes. *Mediators Inflamm.* 2014;2014:131538.
40. Nebbioso M, Federici M, Rusciano D, Evangelista M, Pescosolido N. Oxidative stress in preretinopathic diabetes subjects and antioxidants. *Diabetes Technol Ther.* 2012;14(3):257-263.
41. Haritoglou C, Gerss J, Hammes HP, Kampik A, Ulbig MW. Alpha-lipoic acid for the prevention of diabetic macular edema. *Ophthalmologica.* 2011;226(3):127-137.
42. Kowluru RA, Odenbach S. Effect of long-term administration of alpha-lipoic acid on retinal capillary cell death and the development of retinopathy in diabetic rats. *Diabetes.* 2004;53(12):3233-3238.
43. Lin J, Bierhaus A, Bugert P, et al. Effect of R-(+)-alpha-lipoic acid on experimental diabetic retinopathy. *Diabetologia.* 2006;49(5):1089-1096.
44. Johnsen-Soriano S, Garcia-Pous M, Arnal E, et al. Early lipoic acid intake protects retina of diabetic mice. *Free Radic Res.* 2008;42(7):613-617.
45. Berkowitz BA, Grady EM, Khetarpal N, Patel A, Roberts R. Oxidative stress and light-evoked responses of the posterior segment in a mouse model of diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 2015;56(1):606-615.
46. Kan E, Alici O, Kan EK, Ayar A. Effects of alpha-lipoic acid on retinal ganglion cells, retinal thicknesses, and VEGF production in an experimental model of diabetes. *Int Ophthalmol.* 2017;37(6):1269-1278.
47. Kim YS, Kim M, Choi MY, et al. Alpha-lipoic acid reduces retinal cell death in diabetic mice. *Biochem Biophys Res Commun.* 2018;503(3):1307-1314.
48. Lee SG, Lee CG, Yun IH, Hur DY, Yang JW, Kim HW. Effect of lipoic acid on expression of angiogenic factors in diabetic rat retina. *Clin Exp Ophthalmol.* 2012;40(1):e47-57.
49. Santos JM, Kowluru RA. Role of mitochondria biogenesis in the metabolic memory associated with the continued progression of diabetic retinopathy and its regulation by lipoic acid. *Invest Ophthalmol Vis Sci.* 2011;52(12):8791-8798.
50. Han Y, Wang M, Shen J, et al. Differential efficacy of methylcobalamin and alpha-lipoic acid treatment on symptoms of diabetic peripheral neuropathy. *Minerva Endocrinol.* 2018;43(1):11-18.
51. Agathos E, Tentolouris A, Eleftheriadou I, et al. Effect of alpha-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. *J Int Med Res.* 2018;46(5):1779-1790.

52. Kahler W, Kuklinski B, Ruhlmann C, Plotz C. [Diabetes mellitus--a free radical-associated disease. Results of adjuvant antioxidant supplementation]. *Z Gesamte Inn Med.* 1993;48(5):223-232.
53. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care.* 2006;29(11):2365-2370.
54. Ametov AS, Barinov A, Dyck PJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid: the SYDNEY trial. *Diabetes Care.* 2003;26(3):770-776.
55. Alvarez-Rivera F, Fernandez-Villanueva D, Concheiro A, Alvarez-Lorenzo C. alpha-Lipoic Acid in Soluplus((R)) Polymeric Nanomicelles for Ocular Treatment of Diabetes-Associated Corneal Diseases. *J Pharm Sci.* 2016;105(9):2855-2863.
56. Scripsema NK, Hu DN, Rosen RB. Lutein, Zeaxanthin, and meso-Zeaxanthin in the Clinical Management of Eye Disease. *J Ophthalmol.* 2015;2015:865179.
57. Bungau S, Abdel-Daim MM, Tit DM, et al. Health Benefits of Polyphenols and Carotenoids in Age-Related Eye Diseases. *Oxid Med Cell Longev.* 2019;2019:9783429.
58. Zhang PC, Wu CR, Wang ZL, et al. Effect of lutein supplementation on visual function in nonproliferative diabetic retinopathy. *Asia Pac J Clin Nutr.* 2017;26(3):406-411.
59. Hu BJ, Hu YN, Lin S, Ma WJ, Li XR. Application of Lutein and Zeaxanthin in nonproliferative diabetic retinopathy. *Int J Ophthalmol.* 2011;4(3):303-306.
60. Moschos MM, Dettoraki M, Tsatsos M, Kitsos G, Kalogeropoulos C. Effect of carotenoids dietary supplementation on macular function in diabetic patients. *Eye Vis (Lond).* 2017;4:23.
61. Yang X, Huo F, Liu B, et al. Crocin Inhibits Oxidative Stress and Pro-inflammatory Response of Microglial Cells Associated with Diabetic Retinopathy Through the Activation of PI3K/Akt Signaling Pathway. *J Mol Neurosci.* 2017;61(4):581-589.
62. Ishizuka F, Shimazawa M, Umigai N, et al. Crocetin, a carotenoid derivative, inhibits retinal ischemic damage in mice. *Eur J Pharmacol.* 2013;703(1-3):1-10.
63. Chen L, Qi Y, Yang X. Neuroprotective effects of crocin against oxidative stress induced by ischemia/reperfusion injury in rat retina. *Ophthalmic Res.* 2015;54(3):157-168.
64. Sepahi S, Mohajeri SA, Hosseini SM, et al. Effects of Crocin on Diabetic Maculopathy: A Placebo-Controlled Randomized Clinical Trial. *Am J Ophthalmol.* 2018;190:89-98.
65. Ran Z, Zhang Y, Wen X, Ma J. Curcumin inhibits high glucoseinduced inflammatory injury in human retinal pigment epithelial cells through the ROSPI3K/AKT/mTOR signaling pathway. *Mol Med Rep.* 2019;19(2):1024-1031.
66. Bucolo C, Drago F, Maisto R, et al. Curcumin prevents high glucose damage in retinal pigment epithelial cells through ERK1/2-mediated activation of the Nrf2/HO-1 pathway. *J Cell Physiol.* 2019;234(10):17295-17304.
67. Maugeri A, Mazzone MG, Giuliano F, et al. Curcumin Modulates DNA Methyltransferase Functions in a Cellular Model of Diabetic Retinopathy. *Oxid Med Cell Longev.* 2018;2018:5407482.
68. Li J, Wang P, Ying J, Chen Z, Yu S. Curcumin Attenuates Retinal Vascular Leakage by Inhibiting Calcium/Calmodulin-Dependent Protein Kinase II Activity in Streptozotocin-Induced Diabetes. *Cell Physiol Biochem.* 2016;39(3):1196-1208.

69. Aldebasi YH, Aly SM, Rahmani AH. Therapeutic implications of curcumin in the prevention of diabetic retinopathy via modulation of anti-oxidant activity and genetic pathways. *Int J Physiol Pathophysiol Pharmacol.* 2013;5(4):194-202.
70. Mrudula T, Suryanarayana P, Srinivas PN, Reddy GB. Effect of curcumin on hyperglycemia-induced vascular endothelial growth factor expression in streptozotocin-induced diabetic rat retina. *Biochem Biophys Res Commun.* 2007;361(2):528-532.
71. Yang F, Yu J, Ke F, et al. Curcumin Alleviates Diabetic Retinopathy in Experimental Diabetic Rats. *Ophthalmic Res.* 2018;60(1):43-54.
72. Gupta SK, Kumar B, Nag TC, et al. Curcumin prevents experimental diabetic retinopathy in rats through its hypoglycemic, antioxidant, and anti-inflammatory mechanisms. *J Ocul Pharmacol Ther.* 2011;27(2):123-130.
73. Platania CBM, Fidilio A, Lazzara F, et al. Retinal Protection and Distribution of Curcumin in Vitro and in Vivo. *Front Pharmacol.* 2018;9:670.
74. Mazzolani F, Togni S, Giacomelli L, Eggenhoffner R, Franceschi F. Oral administration of a curcumin-phospholipid formulation (Meriva(R)) for treatment of chronic diabetic macular edema: a pilot study. *Eur Rev Med Pharmacol Sci.* 2018;22(11):3617-3625.
75. Steigerwalt R, Nebbioso M, Appendino G, et al. Meriva(R), a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy. *Panminerva Med.* 2012;54(1 Suppl 4):11-16.
76. Zhao Y, Yu J, Liu J, An X. The Role of Liuwei Dihuang Pills and Ginkgo Leaf Tablets in Treating Diabetic Complications. *Evid Based Complement Alternat Med.* 2016;2016:7931314.
77. Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ. Improved haemorrheological properties by Ginkgo biloba extract (Egb 761) in type 2 diabetes mellitus complicated with retinopathy. *Clin Nutr.* 2004;23(4):615-621.
78. Lanthony P, Cosson JP. [The course of color vision in early diabetic retinopathy treated with Ginkgo biloba extract. A preliminary double-blind versus placebo study]. *J Fr Ophtalmol.* 1988;11(10):671-674.
79. Bucolo C, Marrazzo G, Platania CB, Drago F, Leggio GM, Salomone S. Fortified extract of red berry, Ginkgo biloba, and white willow bark in experimental early diabetic retinopathy. *J Diabetes Res.* 2013;2013:432695.
80. Ou C, Yang YJ, Peng QH. Yiqi Yangyin Huoxue Method in Treating Diabetic Retinopathy: A Systematic Review and Meta-Analysis. *Evid Based Complement Alternat Med.* 2019;2019:6020846.
81. Tarallo S, Beltramo E, Berrone E, Porta M. Human pericyte-endothelial cell interactions in co-culture models mimicking the diabetic retinal microvascular environment. *Acta Diabetol.* 2012;49 Suppl 1:S141-151.
82. Balakumar P, Rohilla A, Krishan P, Solairaj P, Thangathirupathi A. The multifaceted therapeutic potential of benfotiamine. *Pharmacol Res.* 2010;61(6):482-488.
83. Obrenovich ME, Monnier VM. Vitamin B1 blocks damage caused by hyperglycemia. *Sci Aging Knowledge Environ.* 2003;2003(10):Pe6.
84. Berrone E, Beltramo E, Solimine C, Ape AU, Porta M. Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultured in high glucose. *J Biol Chem.* 2006;281(14):9307-9313.

85. Hammes HP, Du X, Edelstein D, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. *Nat Med.* 2003;9(3):294-299.
86. Thornalley PJ. The potential role of thiamine (vitamin B1) in diabetic complications. *Curr Diabetes Rev.* 2005;1(3):287-298.
87. Cinici E, Ahiskali I, Cetin N, et al. Effect of thiamine pyrophosphate on retinopathy induced by hyperglycemia in rats: A biochemical and pathological evaluation. *Indian J Ophthalmol.* 2016;64(6):434-439.
88. Stracke H, Hammes HP, Werkmann D, et al. Efficacy of benfotiamine versus thiamine on function and glycation products of peripheral nerves in diabetic rats. *Exp Clin Endocrinol Diabetes.* 2001;109(6):330-336.
89. Hilbig R, Rahmann H. Comparative autoradiographic investigations on the tissue distribution of benfotiamine versus thiamine in mice. *Arzneimittelforschung.* 1998;48(5):461-468.
90. Du X, Edelstein D, Brownlee M. Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. *Diabetologia.* 2008;51(10):1930-1932.
91. Winkler G, Pal B, Nagybeganyi E, Ory I, Porochnavec M, Kempler P. Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. *Arzneimittelforschung.* 1999;49(3):220-224.
92. Haupt E, Ledermann H, Kopcke W. Benfotiamine in the treatment of diabetic polyneuropathy--a three-week randomized, controlled pilot study (BEDIP study). *Int J Clin Pharmacol Ther.* 2005;43(2):71-77.
93. Stracke H, Lindemann A, Federlin K. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. *Exp Clin Endocrinol Diabetes.* 1996;104(4):311-316.
94. Fraser DA, Diep LM, Hovden IA, et al. The effects of long-term oral benfotiamine supplementation on peripheral nerve function and inflammatory markers in patients with type 1 diabetes: a 24-month, double-blind, randomized, placebo-controlled trial. *Diabetes Care.* 2012;35(5):1095-1097.
95. Alkhalaf A, Kleefstra N, Groenier KH, et al. Effect of benfotiamine on advanced glycation endproducts and markers of endothelial dysfunction and inflammation in diabetic nephropathy. *PLoS One.* 2012;7(7):e40427.
96. Alkhalaf A, Klooster A, van Oeveren W, et al. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care.* 2010;33(7):1598-1601.
97. Miyazawa T, Nakagawa K, Shimasaki S, Nagai R. Lipid glycation and protein glycation in diabetes and atherosclerosis. *Amino Acids.* 2012;42(4):1163-1170.
98. Smolek MK, Notaroberto NF, Jaramillo AG, Pradillo LR. Intervention with vitamins in patients with nonproliferative diabetic retinopathy: a pilot study. *Clin Ophthalmol.* 2013;7:1451-1458.
99. Ma Q, Chen D, Sun HP, Yan N, Xu Y, Pan CW. Regular Chinese Green Tea Consumption is Protective for Diabetic Retinopathy: A Clinic-Based Case-Control Study. *J Diabetes Res.* 2015;2015:231570.

100. Wang L, Sun X, Zhu M, et al. Epigallocatechin-3-gallate stimulates autophagy and reduces apoptosis levels in retinal Muller cells under high-glucose conditions. *Exp Cell Res.* 2019;380(2):149-158.
101. Zhang L, Zhang ZK, Liang S. Epigallocatechin-3-gallate protects retinal vascular endothelial cells from high glucose stress in vitro via the MAPK/ERK-VEGF pathway. *Genet Mol Res.* 2016;15(2).
102. Silva KC, Rosales MA, Hamassaki DE, et al. Green tea is neuroprotective in diabetic retinopathy. *Invest Ophthalmol Vis Sci.* 2013;54(2):1325-1336.
103. Chan CM, Huang JH, Chiang HS, et al. Effects of (-)-epigallocatechin gallate on RPE cell migration and adhesion. *Mol Vis.* 2010;16:586-595.
104. Kim J, Kim CS, Moon MK, Kim JS. Epicatechin breaks preformed glycated serum albumin and reverses the retinal accumulation of advanced glycation end products. *Eur J Pharmacol.* 2015;748:108-114.
105. Lee HS, Jun JH, Jung EH, Koo BA, Kim YS. Epigalloccatechin-3-gallate inhibits ocular neovascularization and vascular permeability in human retinal pigment epithelial and human retinal microvascular endothelial cells via suppression of MMP-9 and VEGF activation. *Molecules.* 2014;19(8):12150-12172.
106. Wang W, Zhang Y, Jin W, Xing Y, Yang A. Catechin Weakens Diabetic Retinopathy by Inhibiting the Expression of NF-kappaB Signaling Pathway-Mediated Inflammatory Factors. *Ann Clin Lab Sci.* 2018;48(5):594-600.
107. Kumar B, Gupta SK, Nag TC, Srivastava S, Saxena R. Green tea prevents hyperglycemia-induced retinal oxidative stress and inflammation in streptozotocin-induced diabetic rats. *Ophthalmic Res.* 2012;47(2):103-108.
108. Sala-Vila A, Diaz-Lopez A, Valls-Pedret C, et al. Dietary Marine omega-3 Fatty Acids and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals With Type 2 Diabetes: Prospective Investigation From the PREDIMED Trial. *JAMA Ophthalmol.* 2016;134(10):1142-1149.
109. Sorokin EL, Smoliakova GP, Bachaldin IL. [Clinical efficacy of eiconol in patients with diabetic retinopathy]. *Vestn Oftalmol.* 1997;113(4):37-39.
110. Tikhonenko M, Lydic TA, Opreanu M, et al. N-3 polyunsaturated Fatty acids prevent diabetic retinopathy by inhibition of retinal vascular damage and enhanced endothelial progenitor cell reparative function. *PLoS One.* 2013;8(1):e55177.
111. Yin Y, Chen F, Wang W, Wang H, Zhang X. Resolvin D1 inhibits inflammatory response in STZ-induced diabetic retinopathy rats: Possible involvement of NLRP3 inflammasome and NF-kappaB signaling pathway. *Mol Vis.* 2017;23:242-250.
112. Bursell SE, Clermont AC, Aiello LP, et al. High-dose vitamin E supplementation normalizes retinal blood flow and creatinine clearance in patients with type 1 diabetes. *Diabetes Care.* 1999;22(8):1245-1251.
113. Chung TW, Yu JJ, Liu DZ. Reducing lipid peroxidation stress of erythrocyte membrane by alpha-tocopherol nicotinate plays an important role in improving blood rheological properties in type 2 diabetic patients with retinopathy. *Diabet Med.* 1998;15(5):380-385.

114. Naseri R, Farzaei F, Haratipour P, et al. Anthocyanins in the Management of Metabolic Syndrome: A Pharmacological and Biopharmaceutical Review. *Front Pharmacol.* 2018;9:1310.
115. Nabavi SF, Habtemariam S, Daglia M, Shafighi N, Barber AJ, Nabavi SM. Anthocyanins as a potential therapy for diabetic retinopathy. *Curr Med Chem.* 2015;22(1):51-58.
116. Putta S, Yarla NS, Kumar KE, et al. Preventive and Therapeutic Potentials of Anthocyanins in Diabetes and Associated Complications. *Curr Med Chem.* 2018;25(39):5347-5371.
117. Huang W, Yan Z, Li D, Ma Y, Zhou J, Sui Z. Antioxidant and Anti-Inflammatory Effects of Blueberry Anthocyanins on High Glucose-Induced Human Retinal Capillary Endothelial Cells. *Oxid Med Cell Longev.* 2018;2018:1862462.
118. Song Y, Huang L, Yu J. Effects of blueberry anthocyanins on retinal oxidative stress and inflammation in diabetes through Nrf2/HO-1 signaling. *J Neuroimmunol.* 2016;301:1-6.
119. Kim J, Kim CS, Lee YM, Sohn E, Jo K, Kim JS. Vaccinium myrtillus extract prevents or delays the onset of diabetes--induced blood-retinal barrier breakdown. *Int J Food Sci Nutr.* 2015;66(2):236-242.
120. Abu-Amero KK, Kondkar AA, Chalam KV. Resveratrol and Ophthalmic Diseases. *Nutrients.* 2016;8(4):200.
121. Toro MD, Nowomiejska K, Avitabile T, et al. Effect of Resveratrol on In Vitro and In Vivo Models of Diabetic Retinophathy: A Systematic Review. *Int J Mol Sci.* 2019;20(14).
122. Popescu M, Bogdan C, Pintea A, Rugina D, Ionescu C. Antiangiogenic cytokines as potential new therapeutic targets for resveratrol in diabetic retinopathy. *Drug Des Devel Ther.* 2018;12:1985-1996.
123. Seong H, Ryu J, Yoo WS, et al. Resveratrol Ameliorates Retinal Ischemia/Reperfusion Injury in C57BL/6J Mice via Downregulation of Caspase-3. *Curr Eye Res.* 2017;42(12):1650-1658.
124. Zeng K, Yang N, Wang D, et al. Resveratrol Prevents Retinal Dysfunction by Regulating Glutamate Transporters, Glutamine Synthetase Expression and Activity in Diabetic Retina. *Neurochem Res.* 2016;41(5):1050-1064.
125. Ghadiri Soufi F, Arbabi-Aval E, Rezaei Kanavi M, Ahmadieh H. Anti-inflammatory properties of resveratrol in the retinas of type 2 diabetic rats. *Clin Exp Pharmacol Physiol.* 2015;42(1):63-68.
126. Yar AS, Menevse S, Dogan I, et al. Investigation of ocular neovascularization-related genes and oxidative stress in diabetic rat eye tissues after resveratrol treatment. *J Med Food.* 2012;15(4):391-398.
127. Soufi FG, Mohammad-Nejad D, Ahmadieh H. Resveratrol improves diabetic retinopathy possibly through oxidative stress - nuclear factor kappaB - apoptosis pathway. *Pharmacol Rep.* 2012;64(6):1505-1514.
128. Kim YH, Kim YS, Roh GS, Choi WS, Cho GJ. Resveratrol blocks diabetes-induced early vascular lesions and vascular endothelial growth factor induction in mouse retinas. *Acta Ophthalmol.* 2012;90(1):e31-37.
129. Sak D, Erdenen F, Muderrisoglu C, et al. The Relationship between Plasma Taurine Levels and Diabetic Complications in Patients with Type 2 Diabetes Mellitus. *Biomolecules.* 2019;9(3).

130. Inam UL, Piao F, Aadil RM, et al. Ameliorative effects of taurine against diabetes: a review. *Amino Acids.* 2018;50(5):487-502.
131. Sarkar P, Basak P, Ghosh S, Kundu M, Sil PC. Prophylactic role of taurine and its derivatives against diabetes mellitus and its related complications. *Food Chem Toxicol.* 2017;110:109-121.
132. Yu X, Xu Z, Mi M, et al. Dietary taurine supplementation ameliorates diabetic retinopathy via anti-excitotoxicity of glutamate in streptozotocin-induced Sprague-Dawley rats. *Neurochem Res.* 2008;33(3):500-507.
133. Di Leo MA, Ghirlanda G, Gentiloni Silveri N, Giardina B, Franconi F, Santini SA. Potential therapeutic effect of antioxidants in experimental diabetic retina: a comparison between chronic taurine and vitamin E plus selenium supplementations. *Free Radic Res.* 2003;37(3):323-330.
134. Kumar B, Gupta SK, Nag TC, et al. Retinal neuroprotective effects of quercetin in streptozotocin-induced diabetic rats. *Exp Eye Res.* 2014;125:193-202.
135. Chen B, He T, Xing Y, Cao T. Effects of quercetin on the expression of MCP-1, MMP-9 and VEGF in rats with diabetic retinopathy. *Exp Ther Med.* 2017;14(6):6022-6026.
136. Lee M, Yun S, Lee H, Yang J. Quercetin Mitigates Inflammatory Responses Induced by Vascular Endothelial Growth Factor in Mouse Retinal Photoreceptor Cells through Suppression of Nuclear Factor Kappa B. *Int J Mol Sci.* 2017;18(11).
137. Ola MS, Ahmed MM, Shams S, Al-Rejaie SS. Neuroprotective effects of quercetin in diabetic rat retina. *Saudi J Biol Sci.* 2017;24(6):1186-1194.
138. Rodriguez Gonzalez-Herrero ME, Ruiz M, Lopez Roman FJ, Marin Sanchez JM, Domingo JC. Supplementation with a highly concentrated docosahexaenoic acid plus xanthophyll carotenoid multivitamin in nonproliferative diabetic retinopathy: prospective controlled study of macular function by fundus microperimetry. *Clin Ophthalmol.* 2018;12:1011-1020.
139. Lafuente M, Ortin L, Argente M, et al. COMBINED INTRAVITREAL RANIBIZUMAB AND ORAL SUPPLEMENTATION WITH DOCOSAHEXAENOIC ACID AND ANTIOXIDANTS FOR DIABETIC MACULAR EDEMA: Two-Year Randomized Single-Blind Controlled Trial Results. *Retina.* 2017;37(7):1277-1286.
140. Roig-Revert MJ, Lleo-Perez A, Zanon-Moreno V, et al. Enhanced Oxidative Stress and Other Potential Biomarkers for Retinopathy in Type 2 Diabetics: Beneficial Effects of the Nutraceutic Supplements. *Biomed Res Int.* 2015;2015:408180.
141. Chous AP, Richer SP, Gerson JD, Kowluru RA. The Diabetes Visual Function Supplement Study (DiVFuSS). *Br J Ophthalmol.* 2016;100(2):227-234.