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PATHOLOGICAL PATHWAY AND PROTECTIVE MECHANISMS OF PHYTOBIOACTIVES USED IN DIABETIC RETINOPATHY: A REVIEW

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ABSTRACT

Diabetes mellitus (DM) is caused by either inadequate or dysfunctional insulin. It is one leading causes of Diabetic retinopathy (DR). Many synthetic medications have serious adverse effects that exacerbate the diabetic patient's condition. The discovery of phytochemicals from medicinal plants offers a promising possibility for the creation of novel therapies for diabetes and its complications including DR. This review highlighted pathological mechanism of DR and also describe numerous plant-derived small compounds (phytochemicals) that have been studied in pre-clinical and clinical settings for their potential to have retinal cytoprotective effects. This also emphasise the mechanism retinal cryoprotection of phytochemicals. The sources were retrieved from various database such as Science Direct, Google Scholar, PubMed, Medline etc. In various studies, phytochemicals reduced inflammation, apoptosis pathways and oxidative stress, which inhibited the development of DR. Numerous phytochemicals, including flavonoids, lignan, glycosides, phytoestrogen etc., inhibited the production of Reactive Oxygen Species (ROS) and downregulation the inflammatory markers such as Interleukin-6(IL-6), Interleukin-1β(IL-1β), and Tumor necrosis factor-α (TNF-α). Overall most of the phytochemicals shows retinal cryoprotection by reducing generation of free radicals and inflammatory mediators.

KEYWORDS: Diabetes, Inflammation, Oxidative stress, Phytochemicals, Retinopathy.

INTRODUCTION

Retinal illnesses are collectively referred to as retinopathy. They frequently affect the small blood vessels (capillaries) feeding the light-sensitive region of the eye, resulting in injury, fluid leakage, or the creation of new crisp blood vessels.[1] The sensory membrane that receives light and transforms it into nerve signals is found inside the eye as part of the retina. In the brain, this impulse generates an image. Vision loss could be partial or total. It can appear gradually or unexpectedly, get better on its own or have permanent negative impacts.[2]

Retinopathy exists in different types, including as:(i) Premature Retinopathy (PR), a fibrous tissue forms behind the lens in this degenerative illness, which is only observed in premature infants and babies with low birth weight. It causes blindness and severe vision impairment.[3] There are several warning signs, such as crossed eyes, near-sightedness, amblyopia (lazy eye), and retinal detachment.[4] (ii) Diabetic Retinopathy, high blood glucose levels cause DR by weakening the retina's tiny blood vessels. As a result, the retina produces more fluid, blood, cholesterol, and other lipids, which causes the macula to thicken and expand.[5] Observing more and more dark spots, poor night vision, fuzzy vision, seeing colours that seem faded or washed out, losing vision and vision that occasionally shifts from blurry to clear are some consequences.[6] (iii) Central Serous Retinopathy, triggered by the accumulation of fluid behind the retina, which can seriously impair vision because the retina is made up of a thin tissue layer.[7] Central vision that is dimmed, blurred, or distorted, straight lines that appear bent, crooked, or irregular in the affected eye, a dark area in the central vision, objects that appear shorter or farther away, and white objects that take on a brownish tinge or seem to duller in colour are all possible symptoms of central serous chorioretinopathy.[8] (iv)Hypertensive Retinopathy, arises when high blood pressure causes damage to the retinal vessels.[9] Eye swelling, double vision associated by headaches, blood vessel rupture, and reduced vision, are a few evidence.[10]

This review explained mainly three pathological pathways of DR which include inflammatory, oxidative stress and apoptosis pathways. This review also emphasises the molecular mechanism of retinal cryoprotection of phytobioactives. These phytochemicals modulate inflammatory, apoptotic and oxidative stress pathways. Numerous phytochemicals, including

flavonoids, lignan, glycosides, phytoestrogen etc., reduces the production of Reactive Oxygen Species and inflammatory markers such as cytokines.

Diabetic Retinopathy

The non-infectious epidemic of the modern world is diabetes mellitus (DM).[11] The WHO currently recognizes DM as a collection of metabolic illnesses characterized by the existence of hyperglycemia caused by insulin release or dysfunction. Individuals with DM who experience chronic hyperglycemia experience destruction, dysfunctional impairment, and insufficiency to a number of body organs, including the eyes, kidneys, nerves, heart, and blood vessels.[12] Diabetes mellitus is a multifactorial disease, chronic illness that requires ongoing treatment and seems to have no permanent treatment to date.[13] Increasing life expectancy in developed countries is one of the reasons why diabetes is more common.[14] However, a longer longevity in those with diabetes mellitus is also associated with a higher risk of chronic microvascular and macrovascular complications brought on by the disease. Vascular complications are currently the leading cause of death and morbidity in people with diabetes mellitus, despite a dramatic drop in the number of deaths directly attributed to this condition.[15] One third of diabetic individuals experience diabetic retinopathy, which is the most common, most dreaded by patients, and the leading cause of visual-specific neurovascular consequences of DM over the past 20 years.[16,17] 80% of blindness in DM patients is triggered by DR,[18,19] which can strike at any stage of the illness.[20]

Severe retinal vascular disease known as DR is marked by the development of new blood vessels, increased vascular permeability, and infarction and congestion in the retina.[21] This is brought on by microangiopathy, which affects the retina's precapillary arteries, capillaries, and venules. Damage arises from internal blood-retinal barrier rupture, which causes microvascular leakage and microvascular occlusion.[22] DR is eye damage caused by prolonged high blood sugar. The walls of the retinal blood vessels weaken, allowing blood to pass through. This causes swelling and vision problems. Over time, new, weaker blood vessels grow, allowing blood to pass through and covering the center of the retina.[23] This is because prolonged exposure to high blood sugar damages the retinal capillaries.[24] Blindness is three times as common in those with diabetes than in the regular populace.[25] It disrupts the retinal vasculature and results in consequences such capillary protrusion, congestion, cotton wool patches, aberrant neovascularization, and microaneurysms.[26]

Sequelae from retinal vascular abnormalities in diabetic retinopathy

Microvascular alterations in the retina can be caused by a chain of disastrous circumstances that are triggered by hyperglycemia. The consistency and functionality of the retina are impacted by these alterations, which eventually cause vision loss. By the time clinically detectable microvascular modifications can be made, significant and occasionally irreparable harm has already been done. Therefore, monitoring the development of diabetic retinopathy requires early molecular alterations detection.[27]

Microaneurysms (MA) – These are the first clinically discernible symptoms, structural deterioration and deformation of the capillary wall.[28] Small sac that can develop as a result of partial capillary wall stretching.[22] They initially make a brief appearance in the fovea and may later vanish.[29]

Haemorrhages – Subretinal dot haemorrhages are the consequence of impaired capillary wall punctures. Precapillary arterioles in the retinal nerve fibre layer are the source of superficial or flame-shaped haemorrhages.[30] The inner nuclear and outer plexiform layers of the retina contain deep haemorrhages, also known as dot and blot haemorrhages, which are more commonly associated with severe hypertension.[22]

Cotton Wool Spots/Soft Exudate – Cotton wool patches, which are axoplasmic aggregates from nerve fibre terminals, are signs of bloodlessness tissue in the nerve fibre layer as a result of the closure of retinal micro vessels.[31] Axonal flow, often referred as axoplasmic transport proceeds in two directions: among somatic cells (the body of neurons) and synapses which transport organelles and cellular components.[32]

Retinal oedema – Microvascular leakage causes retinal inflammation, which is a sign that the inner blood-retinal barrier has broken down. It manifests as thickened, greyish regions of the retina. The macula's swelling, which may resemble a petal-shaped cyst, can seriously impair vision.[22]

IRMA (Intraretinal Microvascular Abnormalities) – It is the linkage between the retinal arterioles and veins that are observable adjacent to the capillary occlusion area and circumvent the capillaries. The retina is where IRMA is found, and it avoids big blood arteries.[30]

When it refers to diabetic retinopathy, there are two broad categories: Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR). Despite the fact believed that several, if not all, of the 30 distinct forms of retinal cells are compromised by diabetes, the extent of the vascular lesion determines the type of retinopathy because it is possible to see the inner retinal vasculature.[33] The main difference between NPDR and PDR is the presence of angiogenesis in PDR.[20] Macular edema can develop at any time as diabetic retinopathy progresses.[34]

NPDR can be split into three different phases: minimal, intermediate, and chronic NPDR, depending on the seriousness of the consequences. This stage is a

persistent damage of the retinal microvascular structures that enables diabetic retinopathy grow pathologically.[35] (i)The initial stage is thought to be mild non-proliferative retinopathy, which is linked to the development of MA. (ii) Moderate non-proliferative retinopathy, where the retina's blood vessels may expand and deform as the disease progresses, losing their capacity to transport blood. (iii) Severe non-proliferative retinopathy causes the retina to receive less blood because more blood vessels are blocked, encouraging the retina to develop new blood vessels. PDR is a highly sophisticated stage of the disease in which the retina's growth factors stimulate the formation of new blood vessels along the retina's inner surface in some vitreous gel that fills the eye.[36]

Molecular Frameworks Implicated In The Diabetic Retinopathy Pathogenesis

Innumerable pathological parameters, especially hyperglycemia and genetic susceptibility, can trigger the onset and advancement of diabetic retinopathy. In diabetes-induced retinal exertion that eventually result in microvascular destruction and retinopathy, several key systems have been identified, together with (i) the polyol pathway, (ii) soreness, (iii) Redox imbalance, (iv) nonenzymatic glycation, (v)protein kinase C (PKC) excitation, and (vi) congenital. Antecedent in the evolution of proliferative retinopathy, these methodologies boost the expression of VEGF.[37,38] while also encouraging the emergence of new blood vessels, enhancing vascular permeability, and driving leukocyte activation and adherence **(Figure 1).**[39,40]

Persistent hyperglycemia: It is thought to be the predominant pathogenic aspect of DR.[41] The polyol pathway as well as other additional glucose metabolism routes are activated by hyperglycemia. Advanced glycation end products (AGEs) are generated as a consequence of PKC activation, non-enzymatic protein glycation and oxidative stress. The stimulation of cytokines, growth factors, and vascular endothelial dysfunction that results from these alternative routes finally causes an increase in vascular permeability and microvascular occlusion. Microvascular blockage triggers retinal ischemia, which encourages the growth of IRMA and neovascularization.[42]

Redox imbalance: Cell and tissue destruction are the outcome of elevated amounts of reactive oxygen species (ROS).[43]

The polyol route: The enzyme aldose reductase in this transform's glucose to sorbitol. Because sorbitol is impermeable, it builds up inside all retinal cells, triggering osmotic deterioration of the cells. Additionally, the reduction process's consumption of NADPH (reduced nicotinamide adenine dinucleotide phosphate) caused enormous oxidative destruction.[44]

PKC: Transduction of signals is involved. Its activation causes abnormalities in the basement membrane and vascular structure, including vascular stasis, capillary occlusion, enhanced vascular permeability, and the generation of angiogenic growth factors.[45]

Non-enzymatic protein glycation: This causes the production of AGEs, which are in charge of altering the extracellular matrix proteins, when reducing sugars react with lipids, free amino acids of nucleic acids, and proteins.[46]

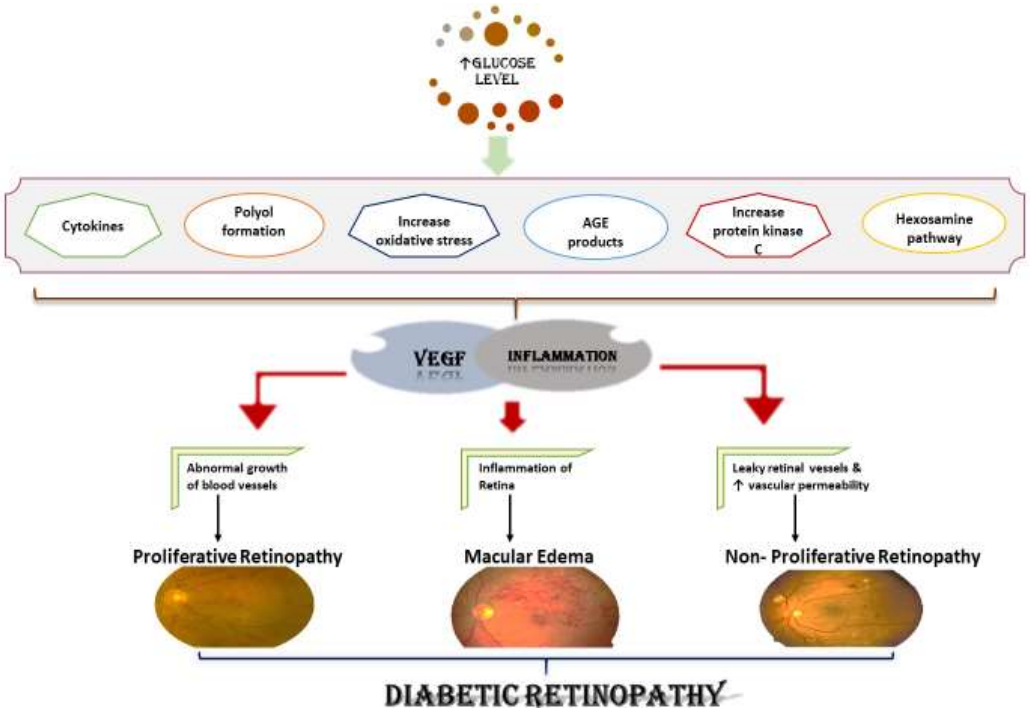

Figure 1: Pathogenesis of DR. (VEGF: Vascular endothelial growth factor).

Phytochemicals For Diabetic Retinopathy Management

Organic natural ingredients called nutraceuticals are enriched with substances including vitamins, antioxidants, minerals, fatty acids, as well as amino acids that can halt the advancement of some disorders or provide a wide range of health improvements. Numerous studies have demonstrated that nutraceuticals provide diverse clinical aspects and defend from a number of ailments.[47] Nutraceuticals are prescribed to treat diabetes because they improve insulin sensitivity, control metabolism, and lower hyperglycemia.[48] One of the most widespread and well-known phytonutrients are terpenoids, alkaloids, glycosides, flavonoids, and tannins.[49] Phytochemicals have well-known antioxidant, antiangiogenic, and anti-inflammatory properties that can be retrieved by food consumption. The majority of phytochemicals are thought to be friendlier treatment options for diabetic retinopathy than pharmaceuticals. In pre-clinical research, phytochemicals controlled oxidative stress, inflammation, and apoptosis pathways to diminish DR **(Figure 2).**[50]

Alkaloids: Alkaloids are secondary plant metabolites that are also present in mammals, microbes, and fungi.[51] These basic alkaloids typically have heterocyclic structures, contain one or more nitrogen atoms, and are derived from amino acids. Alkaloids are categorised according to their pharmacological properties, chemical make-up, biochemical ancestry, and taxonomic origin. For their possible antidiabetic properties, different alkaloids have been taken from a range of herbal plants and tested on diverse animal species.[52] It has been suggested that it is one of the active ingredients in some plants used to treat diabetes.[53] In order to reduce diabetic retinopathy, certain alkaloids include: betaine, cannabidiol, and sinomenine.

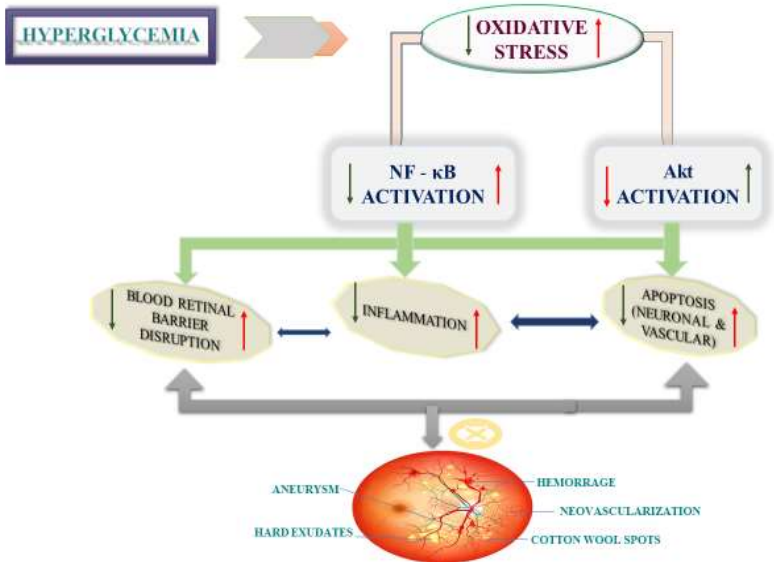

Figure 2: Speculative scenario resulting in diabetic retinopathy from elevated blood glucose levels and the impact of phytochemicals. The green arrow depicts the retardation by phytochemicals, while the red arrow signifies the elevated oxidative stress, inflammation, and apoptotic pathways in DR.

Glycosides: Glycosides are a common type of secondary metabolite found in plants.[54] The aglycone (genin) and glycone (saccharide) components of glycosides are two chemically and functionally distinct sections. A glycosidic bond connects the saccharide and aglycone portions of a glycoside.[55] Several glycosides have been shown to diminish diabetic retinopathy, including: arctiin, aloe-emodin, decursin, gastrodin, gentiopicroside, hesperidin, hesperetin, lithospermic acid B, malvidin, paeoniflorin, physcion 8-O-β-glucopyranoside, pterostilbene, sauchinone, scutellarin, and shikonin.

Flavonoids: Among the most abundant and extensively dispersed classes of organic ingredients inside the plant world are polyphenols, which are scientifically referred to as substances with phenolic structural characteristics. There are many subgroups of phenolic compounds in this group of naturally occurring chemicals, which is very diverse. Fruits and vegetables include flavonoids, a polyphenol subclass with particular biological properties that include anti-inflammatory, antiviral, and antioxidant activities. Flavonoids make up around 60% among all polyphenols.[56] Flavanols, isoflavones, flavones, anthocyanins, flavanones and flavonols are the six types of flavonoids that can be divided based on their chemical structure.[57] Flavonoids can regulate lipid and carbohydrate metabolism, alleviate hyperglycemia, better control inflammatory responses, increase insulin resistance, and enhance β-cell performance, which may assist to delay the onset of long-term chronic diabetes consequences including diabetic retinopathy.[58] The

reduction of diabetic retinopathy by a number of flavonoids has been reported, including: anthocyanins, alpha-mangostin, baicalein, biochanin, curcumin, chrysin, epigallocatechin-3-gallate, eriodictyol, formononetin, genistein, icariin, kaempferol, luteolin, naringin, puerarin, quercetin, resveratrol, rutin, sesamin, silybin, taxifolin, and troxerutin.

Terpenoids: At least 4000 triterpenes are known, and they are produced by the mevalonic acid route. In both plants and animals, terpenes are the building blocks of steroid hormones. These are a group of hydrocarbon substances, such as squalene, that are made up of three terpenes and six isoprene units. Triterpenoids are functionalized triterpenes. One of the largest families of natural products. It (also known as "isoprenoids") has more than 40,000 different chemicals that are involved in both primary and secondary metabolism.[59] These are bioactive substances with strong hypoglycemic effects.[60] Numerous terpenoids have been shown to dampen the risk of developing diabetic retinopathy, including: andrographolide, astaxanthin, carotenoids, dammarenediol-II, β, ε-Carotene-3,3′-diol, sulforaphane, curcumolide, and zerumbone.

Tannins: Innumerable plant species contains tannins, which are polyphenolic macromolecules with a significant molecular weight. Tannins bind and expel proteins as well as a variety of other chemical compounds like alkaloids and amino acids. Condensed tannins and hydrolysable tannins are the two principal types of tannins. Hydrolysable tannins are composed of polyol (D-glucose), hydroxyl moiety, and phenolic acids such as ellagic acid as well as gallic acid. Condensed tannins are a polyphenolic bioflavonoid called polyhydroxy flavan-3-ol. In current history, tannins have received more attention due to the health benefits associated with their antioxidant capacities.[61] Certain tannins can minimize diabetic retinopathy, such as**:** gallic acid, chebulagic acid, chebulinic acid and chlorogenic acid.

The enumeration of alkaloids, glycosides, tannins, flavonoids, and terpenoids along with their origin and mode of action are stated in Table 1.

Table 1: Various phytochemicals effective in DR.

S.no.	Phytochemicals		Source	Mechanism of action	Reference
1.	**Alkaloids**	Betaine	Capsicum, Silybum, Beta vulgaris	↓Akt, VEGF, HIF-1α.	[62]
2.		Cannabidiol	*Cannabis sativa*	Blockage of p38 MAPK. ↓Separation of BBB, ROS, VEGF, TNF-α.	[63]
3.		Sinomenine	*Sinomenium acutum*	↓microglial development, TNF-α, Inflammation of the retina, IL-1β, ROS, IL-6, NF- κB p65.	[64]
4.	**Glycosides**	Aloe emodin	-	↓HIF-1α, PHD-2, expressions in retinal neovascularization of VEGFA.	[65]
5.		Arctiin	*Arctium lappa* L.	↓VEGF, HbA1C. Retinal separation and diminution in retinal edema.	[66]
6.		Decursin	*Angelica gigas*	↓Ocular neovascularization, VEGFR-2 expression. Retinal proliferation, tube development and angiogenesis of retina.	[67]
7.		Gastrodin	*Gastrodia elata*	↓SIRT1/TLR4/NF-κB p65 signaling pathway, NADPH, Nrf2, GCLM, ROS, HO-1 and NQO1, expression of cleaved caspase-3 and cytochrome C. ↑Bcl-2/Bax.	[68]
8.		Gentiopicroside	-	↓Oxidative stress, NF-κB, ICAM-1, IL-1β, GFAP, TNF-α, MDA, expression	[69]

				of VEGF, protein carbonyl, ROS, HDAC overexpression, inflammation in retina. ↑expression of GSH, CAT, PEDF and SOD.	
9.		Hesperidin	Citrus fruits	↓MDA, AR activity, VEGF, IL-1β, ICAM-1, TNF-α, oxidative stress, angiogenesis of retina, inflammation. ↑thickness of the retina, expression of SOD and blood retinal barrier permeability.	[70]
10.		Hesperetin	Citrus fruits	↓PKC-β, widened vessels, Vascular permeability, VEGF, stiffening of BM, angiogenesis of retina. ↓ROS, AQP4, cascape-3, inflammation of retina, TNF-α, GFAP, IL-1β. ↑CAT, SOD and GSH activities in the retina.	[71,72]
11.		Lithospermic acid B	*Salvia miltiorrhiza*	↑capillary BM coat, nerve layer thickness, and ganglion cells. ↓hsCRP, MCP1, VEGF, 8-OHdG and TNF-α, vascular leakage, and arterial sclerosis of capillary.	[73]
12.		Malvidin	*Saccharomyces cerevisiae*	↓Nox4 activity, Mv-3-glc, Mv-3-gal, and Mv.	[74]
13.		Paeoniflorin	*Paeonia lactiflora*	↓MMP-9 activation, inflammation of retina, translocation of NF-κB p65, p-p38 expression, IL-1β, IBA-1. ↑activation of TLR4, thickness of retina, expression of SOCS3 and gliocyte proliferation of retina.	[75]
14.		Physcion8-O-β-glucopyranoside	*Rheum palmatum, Rheum australe,* and *Senna obtusifolia*	↓expression of STAT3 and NORAD, generation of ROS, IL-1 β, TNF-α, apoptosis of cell. ↑expression of miR-125.	[76]
15.		Pterostilbene	*Vitis rupestris, Pterocarpus marsupium*	↓Production of ROS, TNF-α, IL-1β, mRNA, expression of protein and NF-κB. ↑activation of SOD.	[77]
16.		Sauchinone	*Saururus chinensis*	↓Bcl-2, ROS. ↑Akt/Nrf2/HO-1 signaling pathway, CAT, Bax, GPx, SOD.	[78]
17.		Scutellarin	*Scoparia dulcis, Sempervivum*	↓VEGF, activity of NADPH oxidase, ROS,	[79,80]

			ruthenicum	HIF-1α, ERK, FAK, p-Src phosphorylation, proliferation and angiogenesis of retina and development of tube.	
18.		Shikonin	*Lithospermum erythrorhizon*	↓ZO-1, iNOS, MPO, Bax, COX-2, inflammation of retina, damage of retinal cell, vascular permeability, edema.	[81]
19.	**Flavonoids**	Anthocyanins	*Vaccinium myrtillus, Vaccinium virgatum*	↓ROS, VEGF, tight junction proteins loss, breakdown of blood retina barrier, Mv, MV-3-gal, Mv-3-glc, BAE, Akt. ↑SOD, CAT.	[82,74]
20.		α-mangostin	*Garcinia mangostana*	↓MDA, TNF-α, VEGF	[83]
21.		Baicalein	*Scutellaria baicalensis*	↓VEGF, IL-1β, TNF-α, IL-18, GFAP, inflammation of retina, GLC loss, activation of microglial cell, vascular permeability	[84]
22.		Biochanin	*Trifolium pratense*	↓VEGF, ICAM-1, TNF-α, IL-1β, inflammation, angiogenesis of retina. ↑NF- KB.	[85]
23.		Curcumin	*Curcuma longa*	↓VEGF, width of the retinal capillary BM, retinal angiogenesis, 8-OHdG, nitro tyrosine, TNF-α, diameter of vessel, MDA, NF-κB phosphorylation, CaMKII, iNOS, and ICAM-1 expressions, inflammation of retina, IL-1β, HbA1c, vascular leakage of retina, oxidative stress, IL-6, ROS-AKT/mTOR, GFAP. ↑GSH, SOD, T-AOC, CAT, Brn3, Ratio of Bcl-2 to Bax, RecA, Thy-1.	[86-91]
24.		Chrysin	*Passiflora caerulea*	↓VEGF, IGF-1, secretion of AGE, RAGE, HIF-1α, Ang- Tie-2 pathway, neovascularization of retina, ER stress. ↑Thickness of retina, RPE65, PECAM-1, PEDF, RDH5, LRAT, ZO-1 and VE- cadherin junction proteins.	[92,93]
25.		Epigallocatechin-3-Gallate	*Camellia sinensis* L.	↓ERK1/2, MAPK, VEGF.	[94]

26.		Eriodictyol	*Eriodictyon californicum*	↓oxidative stress, eNOS, VEGF, TNF-α, CAM-1, ROS, IL8, inflammation of retina, BAX, cleaved caspase-3. ↑CAT, SOD, GPX, Bcl-2, Nrf2/HO-1 activation.	[95]
27.		Formononetin	*Astragalus membranaceus-s*	↓VEGF, HIF-α, neovascularization of retina.	[96]
28.		Genistein	*Glycine max*	↓VEGF165 and its secretion, ALR, ROS, TNF-α, retinal microglial cell activation, oxidative stress, P38 MAPKs and ERK activation, retinal inflammation and angiogenesis.	[97]
29.		Icariin	*Epimedii Herba*	↓VEGF, RECA. ↑Brn3a, Thy-1.	[98]
30.		Kaempferol	-	↓VEGF, PGF, retinal angiogenesis, Erk1/2, Src, Akt1, P13K expression.	[99]
31.		Luteolin	*Platycodon grandiflorus*	↓VEGF, IL-1β, NF-κB.	[100]
32.		Naringin	-	↓GFAP level, IL-1 β, IL-6, TNF-α, NF-κB p65, oxidative stress, retinal inflammation. ↑GSH, SOD, thickness and cell number of ganglions.	[101]
33.		Puerarin	*Pueraria montana, Radix Puerariae*	↓ROS, NADPH oxidase activity, Rac1, p47phox, NF-κB, 8-OHdG, VEGF, HIF-α.	[102,103]
34.		Quercetin	-	↓MCP-1, ROS, IL-6, apoptosis of cell, NF-κB. ↑miR-29b overexpression.	[104]
35.		Resveratrol	Grapes, and berries	↓oxidative stress, NF-κB, IL-6, TNF-α, COX-2, apoptosis, cell death, basement membrane thickness, vascular hyperpermeability, eNOS, ACE, MM-9 expression.	[105]
36.		Rutin	Onions, Apples, Tea and Red wine	↓Pro- apoptotic pathway, neuronal apoptosis. ↑NGF, BDNF.	[106]
37.		Sesamin	*Sesamum indicum*	↓TNF-α, microglial activation, ICAM-1, iNOS, ROS.	[107]
38.		Silybin	*Silybum marianum*	↓ICAM-1, Retinal vascular leukostasis, retinal capillary deterioration.	[108]
39.		Taxifolin	-	↓tGSH level, MDA, oxidative stress, TNF-α, IL-1β.	[109]

40.		Troxerutin	*Sophora japonica*	↓VEGF, oxidative stress.	[110]
41.	**Terpenoids**	Andrographolide	*Andrographis paniculata*	↓VEGF, TF, retinal angiogenesis, I-κK, I-κB, NF-κBp65, retinal inflammation, Egr-1, TNF-α, IL-6, IL-1β.	[111]
42.		Astaxanthin	Carotenoids present in plants, algae and seafood	↓Oxidative stress, anti-apoptosis pathways.	[112]
43.		Carotenoids	*β-carotene*	↓Oxidative stress, VEGF, ICAM-1, LPO.	[113]
44.		Curcumolide	*Curcuma wenyujin*	↓ICAM-1, retinal vascular leakage, leukostasis, p38 MAPK, TNF-α, NF-κB.	[114]
45.		Dammarenediol-II	*Panax ginseng*	↓VEGF, ROS, formation of stress fibre, microvascular leakage in retina, breakage of vascular endothelial-cadherin.	[115]
46.		β, ε-Carotene-3,3′-diol	-	↓Nitro tyrosine level. ↑ MDA, GSH, GPx.	[116]
47.		Sulforaphane	-	↓Oxidative stress, inflammation, formation of tumour, TNF-α, IL-1β, IL-6, NLRP3, cleaved caspase-1p20, ASC level. ↑GSH, CAT, SOD, ganglion cells count, NQO1, HO-1, Nrf2.	[117]
48.		Zerumbone	*Zingiber zerumbet*	↓Nerve fibres layer, retinal thickness, ganglion cells, IL-6, IL-1β, TNF-α, RAGE, VEGF, NF-κB, VCAM-1.	[118]
49.	**Tannins**	CA, CI, and GA	-	↓Retinal angiogenesis, MMP-9 expression, TNF-α, p38, NF- κB, ERK, IL-6, MCP-1, IL-8, RANTES, MIP-1b, eotaxin. ↑IL-13, IL-10.	[119]
50.		Chlorogenic acid	-	↓VEFGR2, ERK1/2, VEGF, MEK1/2, activity of microglia cell, p38, retinal neovascularization.	[120]

Abbreviations: ↓: Decrease, ↑: Increase, Akt: protein kinase B-1, VEGF: Vascular endothelial growth factor, HIF-1α:Hypoxia-inducible factor-1α, MAPK: Mitogen-activated protein kinases, BBB: Blood retinal barrier, ROS: Reactive oxygen species, TNF-α: Tumor necrosis factor-α, IL: Interleukin, NFκB: Nuclear factor kappa-light-chain-enhancer of activated B cells, PHD-2 :prolyl hydroxylase domain protein 2, HbA1 C: Glycosylated hemoglobin, VEGFR-2:vascular endothelial growth factor receptor, SIRT1: sirtuin 1, TLR4:Toll-like receptor 4, NADPH: nicotinamide adenine dinucleotide phosphate, Nrf2: nuclear factor erythroid 2–related factor 2, GCLM: c-glutamate-cysteine ligase modifier, HO-1: heme-oxygenase-1, NQO1: NADPH quinone oxidoreductase 1, Bcl-2: B-cell lymphoma 2, Bax: BCL-associated X, ICAM-1:Intercellular adhesion molecule-1, GFAP: Glial fibrillary acidic protein, MDA: Malondialdehyde, HDAC: Histone deacetylases, GSH: glutathione peroxidase, SOD: superoxide dismutase, PEDF: pigment epithelium derived factor, AR: aldose

reductase, PKCβ : protein kinase C β, BM: basement membrane, AQP4: aquaporin-4, GFAP: glial fibrillary acidic protein, CAT: catalase, hsCRP: high sensitivity C-reactive protein, MCP-1:Monocyte chemoattractant protein-1, 8-OHdG: 8-hydroxy-2-deoxyguanosine, Nox4: NADPH oxidase 4, Mv-3-glc: malvidin-3-glucoside, Mv-3-gal:malvidin-3-galactoside, Mv: Malvidin, MMP-9: matrix metalloprotease-9, p-p38: Phosphorylated-p38 mitogen-activated protein kinase, Iba-1:Ionized calcium-binding adapter molecule 1, SOCS3: suppressor of cytokine signaling 3, STAT3: signal transducer and activator of transcription 3, NORAD: Non-Coding RNA Activated By DNA Damage, miR-125: MicroRNA-125, GPx: glutathione peroxidase, ERK: Extracellular signal-regulated kinase, FAK: focal adhesion kinase, p-Src: Proto-oncogene tyrosine-protein kinase Src, ZO-1:zonula occludens 2, iNOS: Inducible nitric oxide synthase, MPO: myeloperoxidase, COX-2: cyclooxygenase-2, BAE: blueberry anthocyanin extract, GLC: ganglion cell layer, CaMKII :Calcium/calmodulin-dependent protein kinase II, mTOR :mammalian target of rapamycin, T-AOC: total antioxidant capacity, IGF-1: insulin-like growth factor-I, AGE: advanced glycation end, RAGE: Receptor for Advanced Glycation End products, ER: endoplasmic reticulum, RPE: retinal pigment epithelium, PECAM-1: platelet endothelial cell adhesion molecule-1, RDH5:retinol dehydrogenase 5, LRAT: lecithin retinol acyl transferase, VE-cadherin: Vascular endothelial cadherin, eNOS: Endothelial NOS, ALR: aldose reductase, PGF: placenta growth factor, PI3K : phosphoinositide 3-kinases, NGF: nerve growth factor, BDNF: brain-derived neurotrophic factor, IκB: inhibitor of kappa B, IκK: inhibitor of kinase, Egr1: Early growth response-1, LPO: lipid peroxidation, MAPK: mitogen-activated protein kinase, NLRP3: pyrin domain-containing 3, ASC: adaptor protein apoptosis associated speck-like protein, VCAM-1: vascular cell adhesion molecule-1, MCP-1: monocyte chemoattractant protein-1, MIP-1b: macrophage inflammatory protein-1, RANTES: regulated upon activation, normal T cell expressed and secreted, MEK: mitogen-activated extracellular regulated kinase.

CONCLUSION

The published research showed the evidences of the application of medicinal plants, either as the source of specific extracted constituents or as a combination of various bioactive substances, which exhibits impressive mitigation of cellular damage to the retina or the enhancement of vision.

As per research studies, phytochemicals reduced inflammation, apoptosis pathways and oxidative stress, which inhibited the development of DR. Numerous phytochemicals, including flavonoids, lignan, polyphenols, iridoid glycosides, pyranocoumarin, xanthoid, anthraquinone, sesquiterpene, naphthoquinone, anthocyanins, isothiocyanate, monoterpene glycoside, and isoquinoline, phytoestrogen, inhibited the production of ROS, angiogenic factors, such as PKCβ, HIF-1α and VEGF, and the activity of antioxidant enzyme including MDA, SOD, CAT and NADPH oxidase. Additionally, phytochemicals were found to downregulate the inflammatory markers IL-6, IL-1β, and TNF-α, which have been shown to harm the retina.

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Nil.

CONFLICT OF INTEREST

The authors declared for none conflict of interest.

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