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Beneficial effects of phytochemicals in diabetic retinopathy: experimental and clinical evidence

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Abstract. – Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus and a major preventable cause of blindness. Strict control of blood glucose, blood pressure, and lipid profiles are the pivotal criteria to reduce the risk of developing DR. Although timely intervention with laser photocoagulation therapy could mitigate the progression of DR, it may not significantly improve visual acuity. Therefore, invasive surgical interventions such as vitrectomy are sometimes the only option to treat or manage advanced stages of DR. However, the risk of intra-ocular infections outweighs the benefits of the surgery. Newer therapies such as intraocular injection of anti-vascular endothelial growth factor (VEGF) antibody and steroids serve as a viable option for the treatment of DR. However, several clinical studies that assessed the long-term efficacy and safety of this therapy have yielded inconclusive results. Therefore, there is an urgent need to develop potent and safe drugs for the effective management of DR. In this review, we discuss various plant-derived small molecules (phytochemicals) that have been investigated for retinal cytoprotective effects in pre-clinical and clinical studies. Furthermore, we highlight the caveats on using phytochemicals for the management of DR.

Key Words:
Diabetes, Diabetic complications, Retinopathy, Phytochemicals, Inflammation, Oxidative stress.

Abbreviations

8-OHdG, 8-hydroxy-2-deoxyguanosine; ACE, Angiotensin-converting enzyme; AGEs, Advanced glycation end products; AR, Aldose reductase; BDNF, Brain-derived neurotrophic factor; BRB, Blood retinal barrier; Brn3a, A transcription factor specifically expressed in cells of the developing mammalian nervous system; DR, Diabetic retinopathy; eNOS, Endothelial NOS; ERK, Extracellular signal-regulated kinases; FAK, Focal adhesion kinase; GABA, Gamma-aminobutyric acid; GFAP, Glial fibrillary acidic protein; GLAST, Glutamate transporters; GS, Glutamine synthetase; GSH, Glutathione; HbA_1C, Glycosylated hemoglobin; HIF-1α, Hypoxia-inducible factor-1α; ICAM-1, Intercellular adhesion molecule-1; IL, Interleukin; iNOS, Inducible NOS; MAPK, Mitogen-activated protein kinases; MDA, Malondialdehyde; MMP, Matrix metalloproteinases; MnSOD, Manganese superoxide dismutase; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, Nerve growth factor; NOS, Nitric oxide synthase; NPDR, Non-proliferative diabetic retinopathy; NR1, N-methyl-D:-aspartate receptor subunit 1; Ops, Oscillatory potentials; PDR, Proliferative diabetic retinopathy; RGC, Retinal ganglion cells; ROS, Reactive oxygen species; RSA, Rat serum albumin; Thy-1, A surface glycoprotein of the immunoglobulin superfamily; specifically expressed in RGC; TNF-α,Tumor necrosis factor-α; VEGF, Vascular endothelial growth factor; WNIN, An inbred Wistar rat strain from National Institute of Nutrition Hyderabad, India.

Introduction

Diabetes mellitus has become a worldwide epidemic with a major impact on morbidity and mortality through the microvascular complications of blindness (retinopathy), end-stage renal disease (nephropathy), nerve damage (neuropathy) and lower extremity amputation (ischemic vasculopathy/peripheral artery disease) and macrovascular complications such as cardiovascular disease and stroke[1]. Since these complications pose a major socio-economic burden, it is crucial to understand the mechanisms of how the disease progresses, to devise comprehensive guidelines for early detection and management of diabetes, and to prevent the onset of these debilitating complications. Diabetic retinopathy (DR) is one of the most common diabetic complications, and is the leading cause globally of

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acquired blindness. Clinical and epidemiological studies indicate that 5-7% of patients with type-2 diabetes mellitus could develop DR[2]. Notwithstanding the improved health care and increased lifespan of mankind, the epidemic prevalence of obesity and diabetes, and the occurrence of cardiovascular complications is projected to rise at alarming rates[2]. Currently, there are no approved pharmacological interventions available to treat DR. Although surgical intervention could impede visual loss, it may also cause post-operative complications such as endophthalmitis, and thus, is often not recommended in practice[3]. By understanding the biochemical mechanisms underlying capillary loss, the major process involved in DR, precise pharmacological targets could be defined and used in future treatment strategies[3,4].

Our knowledge about the pathological mechanisms underlying the development of DR is constantly expanding with new inputs from basic and clinical research. Chronic hyperglycemia and other risk factors such as hypertension and hyperlipidemia are thought to initiate a myriad of biochemical and physiological changes, which ultimately promote microvascular damages and retinal dysfunction. Several biochemical alterations in the diabetic milieu culminate the loss of retinal cells, and multiple abnormalities have been proposed to explain how hyperglycemia might cause the progression of retinopathy. For example, increased retinal neural and endothelial cells have been observed in an animal model with some confirmatory observations in human diabetes. Some of the pathways implicated in the development of retinopathy are due to an augmented polyol pathway, protein kinase C (PKC) activation, accumulation of advanced glycation end products (AGEs), oxidative stress, activation of the hexosamine biosynthesis pathway, growth factors and endocannabinoids synthesis[5-9].

The most striking features of DR are the vascular abnormalities that are observed during the fundus examination. The rate of retinal cell loss occurs insidiously in uncontrolled diabetes, and without a regenerative process, the sustained cell loss results in catastrophic retinal tissue damage[10]. To date, there are no diagnostic tools available for the early detection of ongoing cell death, which would aid in early clinical intervention to prevent the progression of human DR. Therefore, development of novel cytoprotective agents that preserve the retinal neurovascular cells against hyperglycemia and its deleterious effects is of paramount significance for the efficient management of DR[10]. Medicinal plants have been used since ancient civilization for treating various ailments. In addition, plants contain diverse chemical constituents (phytochemicals) and they are being extensively investigated for their therapeutic potentials against various diseases affecting mankind[11]. In this review, we discuss the phytochemicals that have been investigated for their ability to ameliorate diabetes-induced retinal tissue injury.

Phytochemicals Investigated for Retinal tissue Cytoprotective Effects in Rodent Models of DR

The chemical structures for phytochemicals that were investigated for their ability to prevent diabetes-induced retinal tissues injury are illustrated in Figure 1. Next, the summary of effects observed when phytochemicals were administered in various rodent models of DR is presented in Table I.

Anthocyanins

Anthocyanins are a type of flavonoids[12] and they have been reported to possess several health benefits[13]. Anthocyanins isolated from *Vaccinium myrtillus* mitigated diabetes-induced blood-retinal barrier breakdown by suppressing vascular endothelial growth factor (VEGF) production and attenuated the loss of tight junction proteins such as zonula occludens-1, occluding, and claudin-5[14]. Similarly, blueberry anthocyanins also inhibited blood-retinal barrier breakdown by suppressing oxidative stress via activation of the Nrf2/HO-1 antioxidant defense system and by down-regulation of pro-inflammatory cytokine and VEGF expression[15].

Arctiin

Arctiin is a lignan extracted from the fruits of *Arctium lappa*[16] and are reported to improve whole body metabolism in rodents[17]. Recently, it was demonstrated that subjecting diabetic animals to treatment with arctiin significantly decreased retinal edema and retinal detachment, which corresponded to diminished VEGF expression in the retina. Furthermore, arctiin was shown to decrease high glucose-induced proliferation of retinal microvascular endothelial cells *in vitro*[17]. However, the precise molecular mechanisms underlying the beneficial effects of arctiin in preventing diabetes-induced retinal tissue injury are unknown.

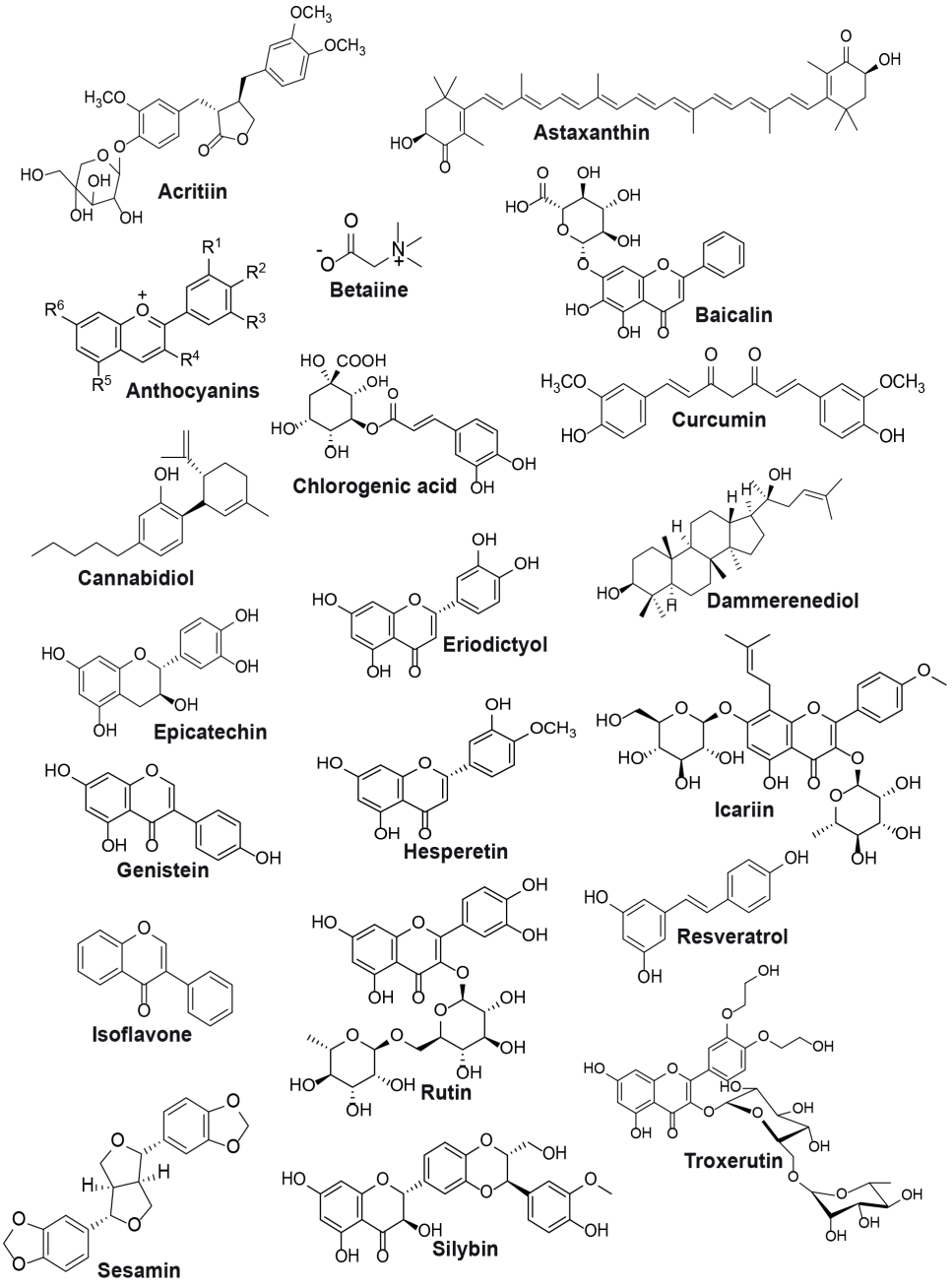

Figure 1. Chemical structures of phytochemicals evaluated for their beneficial effects in thwarting diabetes-induced retinal tissue injury.

Astaxanthin

Astaxanthin is the oxidized ketocarotenoid form of β-carotene, a common pigment extracted mainly from the crustacean family, such as shrimp, crawfish, crabs, and lobsters[18]. Astaxanthin has been shown to possess antioxidant and anti-inflammatory properties and long-term supplementation is associated with a reduced risk for the development of cardiovascular diseases[19]. Astaxanthin was able to ameliorate diabetes-induced retinal tissue injury via attenuation of oxidative stress and augmentation of anti-apoptotic pathways[20]. Furthermore, astaxanthin inhibited hydrogen peroxide-induced cell death and improved mitochondrial respiration in retinal ganglia cells exposed to high glucose. However, the precise biochemical cascade for astaxanthin cytoprotective is unknown.

Table I. Comparison among HAMD, NIM and BI ratings.

Phytochemical	Dose & duration of treatment	Animal model	Effects observed	Reference
Anthocyanins (*Vaccinium myrtillus* extract)	100 $mg.kg^{-1}.day^{-1}$ Oral dose, 6 weeks	STZ-induced Brown Norway (BN) rats	↓ VEGF Prevented the loss of tight junction proteins	14
Arctiin (*Arctium lappa* L.)	30, 90, 270 $mg.kg^{-1}.day^{-1}$ Intra gastric (IG) dose, 16 weeks	Streptozotocin (STZ)-induced Sprague Dawley (SD) rats	↓ HbA1C, VEGF Improved retinal edema, retinal detachment	17
Astaxanthin (carotenoids present in plants, algae and seafood)	25, 50 $mg.kg^{-1}.day^{-1}$ Oral dose, 8 weeks	db/db mice	↓ Oscillatory potentials (Ops), Oxidative stress ↓ apoptosis of retinal ganglion cells (RGC)	20
Baicalein (*Scutellaria baicalensis*)	150 $mg.kg^{-1}$ Oral dose, 24 weeks	STZ-induced SD rats	↓ GFAP, VEGF, IL-18, TNF-α, IL-1β	23
Betaine (capsicum, silybum, Beta vulgaris)	250, 500 $mg.kg^{-1}.day^{-1}$ Oral dose, 14 days	STZ-induced SD rats	↓ VEGF, HIF-1α, Akt	25
Cannabidiol *(Cannabis sativa)*	10 $mg.kg^{-1}$ every 2 days, Intra peritoneally (IP), 4 weeks	STZ-induced SD rats	↓ ROS, TNF-α, VEGF, BRB breakdown Inhibition of p38 MAPK	28
Carotenoids (β-carotene)	10 $mg.kg^{-1}.day^{-1}$ IP, 14 days	STZ-induced SD rats	↓ Oxidative stress	37
Chlorogenic acid (ubiquitously present in plants)	10 and 20 $mg.kg^{-1}.day^{-1}$ IP, 14 days	STZ-induced SD rats	↓ VEGF, BRB breakdown ↑ Occludin, claudin-5, and ZO-1	46
Curcumin *(Curcuma longa)*	0.05% fed with diet, 6 weeks	STZ-induced Lewis rats	↓ IL-1β, VEGF and NF-κB	51
	0.002%, 0.01% fed with AIN-93 diet, 8 weeks	STZ-induced WNIN rats	↓ VEGF	52
	1 $g.\ kg^{-1}$ as Oral suspension, 16 weeks	STZ-induced Wistar rats	↓ TNF-α, VEGF, prevented structural degeneration ↑ Capillary basement membrane thickness	53
	80 $mg.kg^{-1}.day^{-1}$ IP, 3 months	STZ-induced SD rats	↓ MDA, GFAP ↑ GSH	54

Table continued

Table I. *Continued.* Comparison among HAMD, NIM and BI ratings.

Phytochemical	Dose & duration of treatment	Animal model	Effects observed	Reference
Dammarenediol-II (*Panax ginseng*)	25 µg Intravitreal injection, Single dose	STZ-induced C57BL/6J mice	↓ ROS, Stress fiber formation ↓ Vascular endothelial-cadherin disruption	56
Epigallocatechin-3-gallate (*Camellia sinensis*)	20 and 40 mM	High glucose induced human retinal endothelial cell line	↓ MAPK, ERK1/2	60
Eriodictyol (Eriodictyon californicum)	0.1, 1 and 10 $mg.kg^{-1}.day^{-1}$ Oral dose, 10 days	STZ-induced SD rats	↓ LPO ↓ TNFα, VEGF, ICAM-1, and eNOS	63
Genistein (*Glycine max*)	0.25 $mg.kg^{-1}.day^{-1}$, Subcutaneous (SC), 12 weeks	STZ-induced Wistar rats	↓ Retinal GFAP and iNOS	68
Hesperetin (*citrus* fruits)	200 $mg.kg^{-1}.day^{-1}$ Oral dose, 24 weeks	STZ-induced Wistar rats	↓ VEGF, PKC-β	71
Icariin (*Epimedii Herba*)	5 $mg.kg^{-1}.day^{-1}$ Oral dose, 12 weeks	STZ-induced SD rats	↑ Thy-1, Brn3a	74
Isoflavones *(Caesalpinia pulcherrima)*	80, 160 $mg.kg^{-1}.day^{-1}$ Oral dose, 8 weeks	STZ-induced Wistar rats	↑ AR inhibition	76
Luteolin	25- 100 $mg.kg^{-1}.day^{-1}$ Oral dose, 12 weeks	STZ-induced rats	↑ GSH, GPx ↓ MDA, IL-1β, VEGF, NF-κB	78
Polyphenols (Cocoa, tea)	0.12, 2.9 or 22.9 $mg.kg^{-1}.day^{-1}$ Oral dose, 16 weeks	STZ-induced hypertensive male SHR	↓ ROS, PARP-1 ↑ SIRT1	83
Puerarin *(Radix Puerariae)*	80 $mg.kg^{-1}.day^{-1}$ IP, 6 doses, before and after STZ injection	STZ-induced Wistar rats	↓ VEGF, HIF-1α	86
Resveratrol (grapes and berries)	5 $mg.kg^{-1}.day^{-1}$ Oral dose, 4 months	STZ/ Nicotinamide-induced Wistar rats	↓ Oxidative stress ↓ NFκB, apoptosis	91
	20 $mg.kg^{-1}.day^{-1}$ Oral dose, 4 weeks	STZ-induced C57BL/6J mice	↓ Vessel leakage, pericyte loss, VEGF	92
	10 $mg.kg^{-1}.day^{-1}$ IP, 4 weeks	STZ-induced Wistar rats	↓ VEGF, ACE, MMP-9, eNOS	93
	5 $mg.kg^{-1}.day^{-1}$ Oral dose, 4 months	STZ/ Nicotinamide-induced Wistar rats	↓ NF-κB, TNF-α, apoptosis	94
	5, 10 $mg.kg^{-1}.day^{-1}$ Oral dose, 1-7 months	STZ-induced SD rats	↑ GLAST, GS	95
Rutin (onions, apples, tea and red wine)	100 $mg.kg^{-1}.day^{-1}$ Oral dose, 5 weeks	STZ-induced Wistar rats	↑ GSH, BDNF, NGF	101
Sesamin *(Sesamum indicum)*	30 $mg.kg^{-1}$ IP, alternative days, 4 weeks	STZ-induced C57BL/6J mice	↓ Microglia activation and TNF-α ↓ ICAM-1, iNOS	103
Silybin *(Silybum marianum)*	15,30 $mg.kg^{-1}.day^{-1}$ Oral dose, 22 weeks	High fat diet, STZ-induced SD rats	↓ ICAM-1, retinal vascular leukostasis	105
Troxerutin *(Sophora japonica)*	10, 50 $mg.kg^{-1}.day^{-1}$ Oral dose, 3 months	STZ-induced SD rats	↓ VEGF ↓ Oxidative stress	107

Table II. Human clinical studies for evaluating the efficacy of herbal extract supplementation against the development of DR.

Herbal extract	Clinical stage	Sample size	Study type	End point	Reference
Chinese Green Tea (*Camellia sinensis)*	Minimal to severe NPDR, PDR	200	Clinic-based, case-control study	Retinal fundus photographs	76
Danshen-containing Chinese herbal medicine (*Salvia miltiorrhiza)*	Non-proliferative diabetic retinopathy (NPDR)	182	Randomized, double-blind, placebo-controlled multicenter trial	Fluorescence fundus angiography Fundoscopic examination	108
Gnetum africanum and *Dacryodes edulis*	Type-2 diabetic patients with DR	195	Case-control study	8-isoprostane Serum vitamin C	109
Danshen dripping pills	DR of I-III phase	42	Random study	Micro-hemorrhage Micro-aneurysm Mean defect (MD) of visual field	110
Combination of flavonoids with *Centella asiatica* and Melilotus	Diabetic cystoid macular edema (CME) without macular thickening	40	Interventional, controlled study	Visual acuity Central retinal thickness Retinal sensitivity (RS)	111
Ginkgo biloba extract (Egb 761)	Type-2 diabetic patients with DR	25	Preliminary clinical study	Retinal capillary blood flow velocity	112

Baicalein

Baicalein is a natural flavonoid isolated from *Scutellaria baicalensis*, a commonly used traditional Chinese herbal medicine[21] and reported to elicit chemo-preventive actions[22]. In diabetic-rodents, baicalein treatment, ameliorated microglial activation and pro-inflammatory expression[23]. However, detailed mechanistic studies are warranted to understand the beneficial effects of baicalein in diabetic milieu.

Betaine

Betaine is a zwitterionic quaternary ammonium compound, widely distributed in several marine invertebrates, plants, and animals. In the liver, betaine plays a pivotal role in carbon metabolism by serving as a methyl group donor and detoxification of homocysteine[24]. Betaine attenuated diabetes-induced vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF-1α) expression in retina. Paradoxically, there was significant Akt activation observed in the diabetic retinal tissues, which was suppressed by betaine[25]. Therefore, additional studies are warranted to establish the precise molecular mechanism purported for betaine's beneficial role in preventing diabetes-induced retinal tissue injury.

Cannabidiol (CBD)

CBD is the major non-psychotropic component *Cannabis sativa*[26] and possesses antidepressant and anxiolytic properties[27]. Treatment of CBD to diabetic animals was shown to reduce oxidative stress, tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), and intercellular adhesion molecule-1 (ICAM-1) expressions, and prevented retinal cell death and vascular hyperpermeability in retinal tissues. Furthermore, retinal protective effects of CBD were attributed to suppression of p38 MAP kinase in the diabetic retina[28]. In addition, CBD has been demonstrated to ameliorate the development of diabetic cardiomyopathy via mitigation of oxidative stress, inflammation, and cell death pathways[29,30]. Recently, a pilot clinical trial involving subjects with type 2 diabetes mellitus indicated that CBD improved insulin sensitivity and decreased biomarkers for metabolic dysfunction[31]. Considering these findings, CBD has potential for future therapeutic utility to combat diabetic vascular complications.

Carotenoids

Dietary carotenoids provide health benefits by decreasing the risk for the development of cardiovascular diseases[32]. In addition, owing to its strong antioxidant properties, it is widely used in nutraceuticals and cosmetic products[33]. Sevin and Cuendet[34] reported on the use of carotenoids to prevent capillary resistance in diabetes. Thereafter, several studies[35-37] reported on the role of carotenoids in ameliorating DR. The dietary carotenoid zeaxanthin was found to inhibit diabetes-induced retinal oxidative damage and to prevent the elevation of VEGF and ICAM-1 levels[38]. Lutein, another carotenoid, has been shown to decrease oxidative stress and lipid peroxidation (LPO) in diabetic retinal tissues[39-42]. Furthermore, another carotenoid (lycopene) was reported to decrease diabetes-induced oxidative stress in retinal tissues[43].

Chlorogenic Acid (CGA)

Chlorogenic acid (5-caffeoylquinic acid) is a polyphenolic compound, present in coffee, tea, apples, peaches, carrots, blueberries, tomatoes, oilseeds, eggplants, prunes, and cherries[44]. Many studies have linked CGA consumption to a wide range of health benefits, including neuroprotection, cardioprotection, chemo preventions, anti-inflammatory activity, blood pressure control, decreased diet-induced insulin resistance, and anxiolytic effects[45]. First, Shin et al[46] reported that CGA was found to preserve tight junction proteins, and to suppress VEGF production, resulting in the maintenance of blood–retinal barrier integrity. In addition, CGA inhibited VEGF-induced angiogenesis[47], mitigated AGE formation, and mitigated high-glucose induced oxidative stress and inflammation in the diabetic retinal tissues[48].

Curcumin

Curcumin is the sesquiterpene extracted from *Curcuma longa*[49]. Curcumin has been shown to possess antioxidant, anti-inflammatory, and chemopreventive properties[50]. Curcumin treatment to diabetic animals was found to improve antioxidant capacity, and inhibit diabetes-induced elevation of IL-1β, VEGF, and NF-κB activation in retinal tissues[51]. Furthermore, curcumin also decreased pro-inflammatory cytokine expression and prevented structural degeneration and averted capillary basement membrane thickening in diabetic retinas[52,53]. In addition, curcumin inhibited diabetes-induced apoptosis of Müller cells, prevented the down-regulation of glutamine synthetase (GS), and decreased glial fibrillary acidic protein (GFAP) in diabetic retina[54].

Dammarenediol-II

Dammarenediol-II is a triterpene extracted from the popular medicinal plant *Panax ginseng*[55]. Dammarenediol-II was found to inhibit VEGF-induced intracellular reactive oxygen species (ROS) generation, stress fiber formation, and vascular endothelial-cadherin disruption in human umbilical vein endothelial cells (HUVECs), and prevented microvascular leakage in the retina[56]. However, the precise mechanism for dammarenediol-II's retinal protective effect in the diabetic environment is not clear. Since HUVECs are derived from a macro vessel, they are not considered an appropriate model system to investigate the effect of hyperglycemia-induced alterations in the retinal microvasculature.

Epigallocatechin-3-Gallate (EGCG)

EGCG is a flavonoid found in variety of vegetable foods and beverages, such as fruits, chocolate, wine, tea, but mainly in green tea (*Camellia sinensis* L.), accounting for more than 50% of total green tea polyphenols[57] and has great potential in cancer prevention[58]. EGCG was shown to decrease extracellular regulated kinase (ERK)1/2 and inhibit VEGF[59,60].

Eriodictyol

Eriodictyol, is a flavonoid extracted from North American plant *Eriodictyon californicum* and from Chinese herb *Dracocephalum ruppestre* and its glycoside, eriodictyol 7-O-rutinoside, is present in lemon fruit[61]. Eriodictyol was demonstrated to protect retinal endothelial cells against high-glucose induced cell death and also attenuated β-amyloid peptide-induced oxidative stress-mediated cell death in retinal neurons[62]. Furthermore, eriodictyol was found to inhibit the production of TNF-α, ICAM-1, VEGF, and eNOS in diabetic retinal tissues[63].

Genistein

Genistein (4'5, 7-trihydroxyisoflavone) occurs as a glycoside in *Leguminosae* family plants, which includes the soybean (*Glycine max*)[64]. Genistein was found to inhibit retinal vascular leakage in experimentally induced diabetic rats[65]. In addition, genistein combined with other polysaccharides improved the antioxidant status in diabetic retina[66]. Furthermore, genistein attenuated

the release of TNF-α and inhibited ERK and p38 MAPK activation[67]. In addition, genistein was found to protect against gliopathy and vasculopathy of diabetic retinas by decreasing GFAP and iNOS expression[68].

Hesperetin (HST)

Hesperetin, a flavanone glycoside (a subclass of flavonoids), is found abundantly in citrus fruits[69,70]. Kumar et al. have reported that HST was found to inhibit the expression of VEGF and PKC-β in diabetic retina[71]. In addition, HST treatment suppressed diabetes-induced caspase-3 activation, glial activation, aquaporin-4 (AQP4) expression and retinal oxidative stress[72].

Icariin

Icariin (an 8-prenyl derivative of kaempferol 3,7-O-diglucoside) is the most abundant constituent and chosen as the chemical marker for quality control of *Herba Epimedii* in Chinese Pharmacopeia and has extensive clinical indications, especially for the treatment of sexual dysfunction and osteoporosis[73]. Icariin was demonstrated to suppress the upregulation of rat endothelial cell antigen-1 (RECA), VEGF, and retinal ganglion cell-specific markers (Thy-1 and Brn3a) in the diabetic retina[74].

Isoflavones

Isoflavones belong to the "phytoestrogen" class, mainly found in soybeans, and legumes[75]. Isoflavones isolated from *Caesalpinia pulcherrima* were shown to reduce oxidative stress and inhibit aldose reductase (AR) activity in the diabetic retinal tissues[76].

Luteolin

Luteolin is a natural flavonoid isolated from *Platycodon grandiflorus* which is widely used in Asian traditional herbal medicine and also found in dietary sources such as celery, broccoli, green pepper, parsley, thyme, dandelion, perilla, chamomile tea, carrots, olive oil, peppermint, rosemary, navel oranges, and oregano[77]. Luteolin was shown to inhibit diabetes-induced elevation of IL-1β, VEGF, and NF-κB expression in the retina of diabetic rodents[78].

Polyphenols

Polyphenols constitute the active substances found in blackberries, red grapes, apricots, eggplants, and popular beverages, such as coffee, cocoa, and green tea. Polyphenols modulate the activity of a wide range of enzymes and cell receptors[79]. Polyphenols from finger millet (*Eleusine coracana*) were found to inhibit AR and to prevent cataractogenesis[80]. Polyphenols from red wine were shown to reduce retinal oxidative and nitrative stress[81]. Polyphenols from green tea have been shown to decrease glial fibrillary acidic protein (GFAP) expression and oxidative stress in the retina[82]. In addition, polyphenols from cocoa were also found to reduce oxidative stress, PARP activation, and augmented SIRT1 activity in diabetic retinas[83].

Puerarin

Puerarin (isoflavone-C-glucoside) is derived from *Pueraria lobata* root. In traditional Chinese medicine, it has been suggested to be useful in the treatment of cardiovascular and cerebrovascular diseases, diabetes mellitus and diabetic complications, osteonecrosis, Parkinson's disease, Alzheimer's disease, endometriosis, and cancer[84]. First, Ren et al[85] have reported that puerarin improved the retinal microvascular rheology, and improved microcirculation in retinal tissues. Furthermore, puerarin was shown to down-regulate streptozotocin (STZ) induced-VEGF and HIF-1α in experimental DR[86]. In addition, puerarin decreased the apoptosis of retinal pigment epithelium (RPE) cells in diabetic rats by reducing peroxynitrite levels and iNOS expression[87]. Kim et al[88] have shown that, puerarin ameliorated retinal microvascular dysfunction, by inhibiting AGE-induced pericyte apoptosis by interfering with the NADPH oxidase-related ROS generation pathways and blocking NF-κB activation.

Resveratrol (RVT)

Resveratrol (3, 4', 5-trihydroxystilbene) is a natural polyphenolic phytoalexin that is mainly found in grapes and fruit berries[89] and reported to be useful in the treatment of neurodegenerative diseases, diabetes and cardiac ailments[90]. RVT was found to suppress diabetes-induced oxidative stress, NF-κB activation, pro-inflammatory cytokines expression, and apoptosis in the retinal tissues. Furthermore, RVT treatment also prevented diabetes-induced neuronal cell death, vascular hyperpermeability, and basement membrane thickening. These effects were in part attributed to the diminution of ACE and MMP-9 expression and augmentation of eNOS. In addition, RVT also improved the retinal nerve function as assessed by electroretinogram (ERG)[91-95].

Rutin

Rutin (3,30,40,5,7-pentahydroxyflavone-3-rhamnoglucoside) is a flavonoid found in many plants, such as buckwheat, passion flower, apple, and tea[96] and possesses multi- spectrum pharmacological benefits for the treatment of various chronic diseases such as cancer, diabetes mellitus, hypertension, and hypercholesterolemia[97]. Several studies have reported on the efficacy of rutin for eye diseases[98-100]. Ola et al. have shown that providing rutin treatment to diabetic animals enhanced brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), suppressed pro-apoptotic pathways, and prevented neuronal apoptosis in retinal tissues[101].

Sesamin

Sesamin, an antioxidant lignan, is obtained from oilseed *Sesamum indicum*[102] and is synthesized from shikimic acid via the phenylpropanoid pathway, then metabolized to enterolignans, which play a pivotal role in protection against several hormone-related diseases[102]. Sesamin was found to inhibit the progression of diabetic retinal injury by suppressing pro-inflammatory cytokine expression and microglia activation. However, the precise molecular mechanism is not evident from this study[103].

Silybin

Silybin, a bioactive polyphenolic flavonoid extracted from milk thistle seeds (*Silybum marianum*), has been used as a traditional drug for over 2000 years to treat a range of liver diseases[104]. Silybin was found to prevent the obliteration of retinal capillaries and retinal vascular leukostasis via suppression of ICAM-1 expression[105].

Troxerutin (TX)

Troxerutin (Vitamin P4) is a flavonoid best known for its radioprotective and antioxidant properties[106]. Administration of TX to diabetic animals was found to attenuate oxidative stress and VEGF expression in the retina; however, detailed mechanistic studies were not performed and therefore further confirmatory studies are warranted to ascertain TX's beneficial effects in the prevention of diabetes-induced retinal tissue injury[107].

Human Clinical Studies Undertaken to Investigate the Beneficial Effects of Phytochemical and or Herbal Extracts on the Progression of Diabetic Retinopathy

The various herbal extracts and phytochemicals that were investigated for their ability to thwart the development of DR are presented in Table II. A randomized double-blind clinical study assessed the efficacy of the Chinese herbal[108] extract *Salvia miltiorrhiza* in subjects with non-proliferative DR (NPDR). Results suggested that *Salvia miltiorrhiza* treatment for 24 weeks prevented diabetes-induced alterations in the retinal anatomy. In a central African cohort[109], it was demonstrated that supplementation of herbal extracts had profound antioxidant augmenting effects in subjects with DR. However, the direct effect of herbal extract supplementation on various clinical endpoints for the amelioration of DR was not evident from this study. Similarly, other clinical trials[110-113] also reported that supplementation with herbal extracts led to significantly positive outcomes pertaining to the clinical end points evaluated for progression of DR.

Limitations

Phytochemicals attenuated the development of DR in pre-clinical studies via suppression of oxidative stress, inflammation, and apoptosis pathways (Figure 2). Invariably, all studies have reported the apparent protective effects of phytochemicals against diabetes-induced retinal tissue injury in pre-clinical experiments and in human clinical trials. However, the major impediment to using phytochemicals for the management of DR is the lack of significant bioavailability in human subjects[114,115]. In fact, a recent clinical trial[116] revealed that RVT supplementation to subjects with type 2 diabetes mellitus suppressed the metformin/insulin sensitizing action owing to drug-drug interactions, and had no effect in improving hepatic glucose disposition or peripheral insulin sensitivity.

Conclusions

Before presenting phytochemicals as candidates for future drug development against DR, we should consider the potential drug-drug interactions, which could curtail the therapeutic action of these drugs. Although, clinical studies have been undertaken to establish the efficacy and safety of herbal extracts for the management of DR, these studies were seldom replicated in other locations. Also, the selectivity and specificity of phytochemical mode of actions and their molecular drug targets in DR is yet to be established, meaning that there is no surrogate

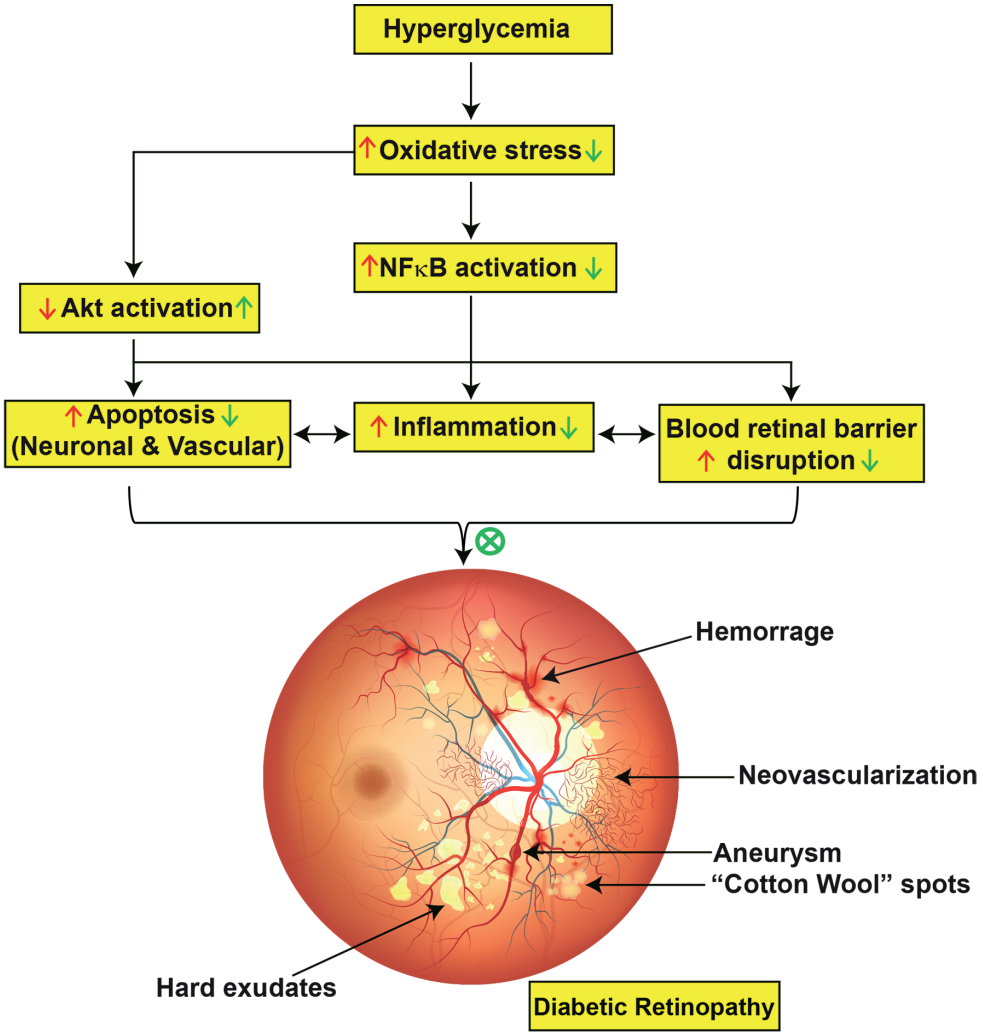

Figure 2. Depiction of the pathways suggested for the development of DR and mitigated by phytochemicals. The red arrow indicates the exaggerated oxidative stress, inflammation, and apoptotic pathways in DR, while the green arrow represents the attenuation by phytochemicals.

marker available to assess the prognosis of DR. Furthermore, the pathophysiology of DR is not completely established and with the failure of anti-VEGF based therapy for DR[117], it is apparent that more basic clinical research is required. This research should identify early biomarkers for retinal tissue damage, and purported specific molecular/biochemical alterations, and attempt to use this information to develop new potent drugs for the efficient management of DR.

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Author contributions

MR and SO conceptualized the review, searched the literature, drafted, edited, and prepared the final version of the manuscript. BV reviewed literature and drafted the manuscript. BS drew the chemical structures of phytochemicals.

Conflict of interest

The authors declare no conflicts of interest.

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