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Diabetic Retinopathy: An Insight into Clinical Features, Therapeutic Approaches, and Implications

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder that affects the heart, brain, eye, and other organs. Diabetic microvascular complications includes retinopathy, nephropathy, and neuropathy. Diabetic retinopathy is a multifactorial disease that develops as a consequence of microvascular complications, which causes damage to the retina by damaging the ocular fundus which further leads to visual loss.

Purpose: Pharmacological and non-pharmacological treatment works to prevent, delay or reduce vision loss. Non-pharmacological treatment include nutraceuticals (they have anti-inflammatory and antioxidant property) and pharmacological treatment includes anti-VEGF agents, corticosteroids, and specific moieties. Treatment with nutraceuticals in the early stages of diabetic retinopathy could be a viable option for intervening before the disease progresses.

Conclusion: This review briefly elucidates the emerging condition of diabetic retinopathy from epidemiological, pathophysiological, and therapeutic aspects including the emerging uses of nutraceuticals in diabetic retinopathy. If we control glucose and blood pressure levels in diabetic patients, it may halt the progression and development of diabetic retinopathy.

1. Introduction

Diabetes mellitus is a metabolic condition that is associated with chronic hyperglycaemia with carbohydrate, fat, and protein metabolism disturbances induced by insulin secretion defects, action on insulin, or both (Alberti, 1998; Chawla, 2016). Chronic hyperglycaemia causes long-term injury and impairment in organ functions, which further lead to organ failure such as eyes, heart, kidney and has severe effect on nerves and blood vessels (American Diabetes Association, 2013). In India, 95% of adults have diabetes mellitus [T2DM]. India is known to be one of the epicenteres of the global diabetes mellitus outbreak and has the world's second-largest number of patients suffering from this condition (Unnikrishnan, 2016). DM is classified into different types i.e. type 1 DM (β-cell destruction and generally results in (insulin deficiency) and another type is type 2 DM (insulin resistance with insulin deficiency. Furthermore, diabetes mellitus leads to complications and cause severe damage to the retina termed diabetic retinopathy (DR), the primary prevalent etiological factor of visual impairment among adults in developing countries (Heng et al., 2013; Andreasson, 2018). DR is the clinically evident demonstration in the ocular fundus (inner lining of eye) of long-term diabetes. Its existence indicates the combination of the duration of the length of the condition and the extent of glycaemic regulation. Though better systemic regulation of blood glucose and blood pressure may prolong onset and progression, almost all patients with ample disease duration will be affected by DR (Hendrick, 2015). There is a severe ocular complication in diabetic retinopathy (Cheung et al. 2010), known as diabetic macular oedema (DME), characterized as retinal thickening due to microaneurysms involving the middle of the macula (Bandello et al. 2010). Epidemiological, genetic, and experimental research reinforced the understanding of the pathophysiology underlying diabetic retinopathy (Cheung, 2010). There are a variety of documented diabetes complications, classified into microvascular and macrovascular complications, including retinopathy, nephropathy, peripheral neuropathy, and autonomic neuropathy (Andreasson, 2018).The involvement of diabetic retinopathy also represents an elevated risk of life-threatening systemic vascular complications, in addition to its effects on vision (Cheung, 2010; Andreasson, 2018).

Diabetes affects more than 180 million people globally, according to the World Health Organization (WHO) (Bandello et al., 2010; Cohen, 2016). Diabetic retinopathy which is a microvascular complication of diabetes has a global

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prevalence of 40%, with 93 million diabetic retinopathy people and proliferative retinopathy people accounting for 17 million, 28 million people from vision-threatening diabetic retinopathy (VTDR) and 21 million people with diabetic macular oedema (Yau et al., 2012; Heng et al., 2013).The frequency of retinopathy and nephropathy with type 1 DM people has declined from the last 35 years as a result of improved medical therapy, but the prospects are not encouraging (Bandello et al., 2010; Cohen, 2016; Morrison et al., 2016).

Type II diabetes incidence results suggest that 2-8.2% with diabetes suffered from macular oedema 5 years after a history of T2DM (Bandello et al., 2010). In the United States, about 500 million people have clinically relevant DME and about "700" million have proliferative DR (Bandello et al., 2010; Cohen, 2016). Insulin-treated patients had a greater incidence of macular oedema; after the 15 years of diagnosis, macular oedema occurred in 20% of T2DM patients and 18% of T1DM patients on insulin, while macular oedema occurred in about 12% T1DM & T2DM patients not taking insulin (Bandello et al., 2010).

2. Classification Based on Types of Diabetic Retinopathy

Diabetic retinopathy is classified into several types which are discussed in Table 1.

Table 1: Describes diabetes retinopathy types based on severity (Lightman, 2003; Cheung, 2010; Heng et al., 2013).

No retinopathy	There is no evidence of microvascular lesions
Background retinopathy [Mild and moderate non-proliferative]	The mildest type of retinopathy is background retinopathy and can be associated with normal vision. Micro aneurysm, Venous loop, Retinal haemorrhage (s) are seen; in the presence of other non-referable characteristics of diabetic retinopathy
Pre-proliferative or Severe NPDR[non-proliferative diabetic retinopathy]	Signs of significant ischemia in the retina are seen. Key symptoms are venous beading, a distinctive sign; arterial thinning and occlusion shown as white lines; intraretinal microvascular defects that arise when there is ischemia as a result of vascular remodelling); and growing spots of cotton wool
Proliferative diabetic retinopathy (Non-high-risk and high-risk characteristic proliferative diabetic retinopathy)	Signs are mild NVD (Neovascularisation of the optic disc) with vitreous haemorrhage, moderate-to-severe NVD with or without vitreous haemorrhage; moderate NVE (Neovascularisation of elsewhere) with vitreous haemorrhage; moderate-to-severe NVD with or without vitreous haemorrhage; "moderate NVE with vitreous haemorrhage"
Clinically significant macular oedema	Retinal thickening from the centre of the macula within 500 μm; rough exudates from the centre of the macula within 500 μm with adjacent retinal thickening; retinal thickening from the centre of the macula of more than one optic disc region within one optic disc diameter;

3. Pathogenesis

A sequence of metabolic and physiological modifications that eventually contribute to microvascular disruption and retinal dysfunction is assumed to be initiated by prolonged exposure to hyperglycaemia and other causal risk factors (e.g., hypertension, kidney disease) (Cheung et al. 2010). The pathogenesis of diabetic retinopathy has been linked to a number of interconnected biochemical pathways associated with hyperglycaemia, including the production of advanced glycated end products, polyol aggregation, oxidative stress, renin-angiotensin system upregulation, protein kinase C activation and involvement of vascular endothelial growth factor [VEGF] (Heng et al., 2013; Hendrick, 2015). VEGF is a pathological precursor of vascular leakage promoting the growth of new blood vessels, and forms the basis of vision-threatening disease treatment (Cheung, 2013; Hendrick, 2015). These cytokines stimulate many signalling pathways and are primarily responsible for the two major vision-threatening consequences of diabetic retinopathy: the symptoms of retinal neovascularization and macular oedema resulting from the breakdown in the centre of the retina of the blood-retinal barrier (Heng et al., 2013).

Because of hyperglycaemia, these mechanisms contribute to the development of microvascular damage, enhanced capillary permeability, vascular occlusion, and weakening of support structures (Hendrick, 2015). Chronic hyperglycaemia leads to damage of pericytes and endothelial cells resulting in vascular endothelial dysfunction. Micro aneurysms, intraretinal haemorrhages, and focal areas of retinal ischemia (cotton-wool spots) are then formed in

the retina, this stage is known as non-proliferative diabetic retinopathy (NPDR)(Garg, 2009). Thickening of Vascular basement membrane (vBM) in DR might be due to the increase in fibronectin, collagen, and laminin resulting in alterations in micro environmental components that enhance the growth, survival, and function of pericytes and endothelial cells (Whitehead et al., 2018).

Inflammation is progressively shown to have a significant role in the pathogenesis of diabetic retinopathy and includes upregulation of several inflammatory mediators in diabetes in response to hyperglycaemia and other imbalances (e.g. dyslipidaemia), causing para inflammatory responses that can lead to irregular leukocyte-endothelial interactions and consequently retinal microvascular disruption (Cheung, 2010). In the early stages of diabetic retinopathy development, the micro aneurysms appear as balloon-like capillary wall protrusions and are considered to activate inflammatory cascade that promotes the damage of endothelial lining. Late-stage microaneurysms are often sclerotic and are sometimes relatedto regions of severe capillary degeneration in the absence of an endothelial lining. Pathogenesis of DR is briefly figured in Figure 1 (Cheung, 2010; Whitehead et al., 2018).

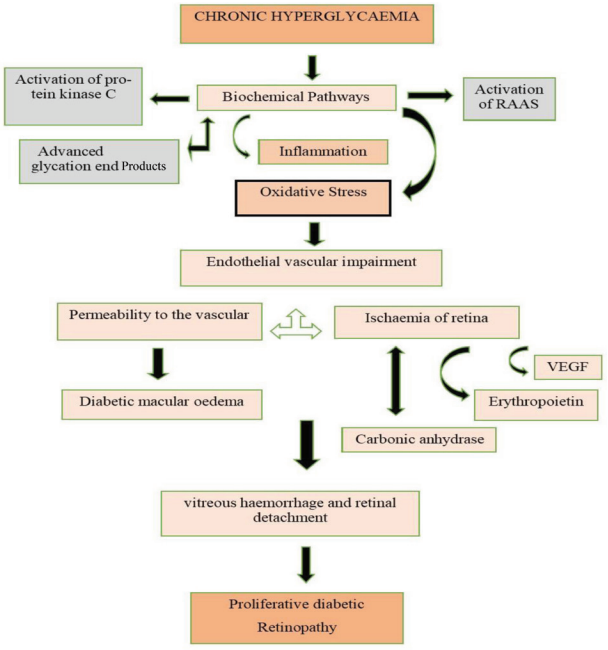

Figure 1: Brief illustration of the pathogenesis of Diabetic Retinopathy (Cheung, 2010, Whitehead et al., 2018).

4. Risk Factors Associated with Diabetic Retinopathy

The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) is probably the largest and oldest DR survey to date, with its prevalence, incidence, and associated risk factors (Porta et al. 2002). Diabetes severity and duration, hypertension, involvement of other complications, anaemia, hyperlipidaemia, insulin resistance and deficiency, nephropathy, type 1 diabetes, and a family history of DR have long been recognized as clinical risk factors for DR (Hendrich, 2015; Cohen, 2016). Retinopathy is found rare for type 1 diabetes before puberty, but the history of diabetes is long; in adults retinopathy is rare in the first 5 years, but 25 to 50 percent of patients will show such symptoms after 10 to 15 years, 75 to 95 percent after 15 years, and 95 percent after 30 years (Lightman, 2003). Few studies report the younger age of onset of DM as a risk factor towards the progression of DR, elevated haemoglobin A1c, in T2DM, insulin use in pregnancy, baseline occurrence of diabetic macular oedema (DME) (Morrison et al., 2016; Kwan, 2019). The existence of glycated haemoglobin (HbA1c), an advanced glycation end product, is an indicator of chronically increased glucose (AGE), a mean value of 7.0 would increase the risk of a patient developing diabetic retinopathy (Kwan, 2019). In DME, duration of diabetes, increased glycosylated haemoglobin A1c, hypertension, degree of metabolic regulation, DR severity, low socioeconomic status, and older age are the recorded risk factors for the incidence and DME progression, most of which are found in studies such as the "WESDR and the UK Prospective Diabetes Study" (Bandello et al., 2010). In pregnancy, it was found that pregnancy itself was an independent risk factor for the progression and severity of DR. During pregnancy, other risk factors (i.e., low glycaemic regulation, length of diabetes, hypertension, etc.) for the development of DR are the same as reported in the other diabetic people (Morrison et al., 2016).

5. Clinical Assessment

Diabetic retinopathy is clinically characterized in a person with diabetes mellitus as the appearance of typical retinal microvascular signs. The goal of clinical assessment should be to identify these severe ocular symptoms and to determine the likelihood of progression to vision-threatening diseases in their absence (Cheung, 2010). Clinically, there is a range of symptomatic ailments in diabetic macular oedema or proliferative DR and variability is prevalent between patients. Patients are usually asymptomatic during the early stages of the disease but develop over time to experience micro aneurysms, haemorrhages, and microvascular intraretinal anomalies (Whitehead et al., 2018). Direct ophthalmoscopy eye examination allows for an appropriate assessment of the symptoms of diabetic retinopathy via-"slit-lamp bio microscopy" using a condensing lens. In addition, evaluation of the peripheral fundus is necessary

to avoid peripheral retinal ischemia and neovascularization, especially in population of T1DM. A systematic evaluation of patient with newly diagnosed diabetic retinopathy is also recommended by physicians (Cheung, 2010).

Diabetic retinopathy screening must be conducted in the scope of the availability of effective care combined with accurate diagnostic methods (Lightman, 2003). For "screening, diagnosis, and monitoring of diabetic retinopathy," ophthalmic imaging modalities are increasing. Retinal photography has been used as a beneficial screening technique for diabetic retinopathy especially when access to ophthalmologists is difficult (Cheung et al. 2010). For cases with "active proliferative diabetic retinopathy (R3a)", patients should be monitored within a period of 4 weeks in an eye clinic and treated with laser pan-retinal photocoagulation within a further 2 weeks if required. In"M1 (referable maculopathy), R2 (referable retinopathy) or treated non-active lesion proliferative diabetic retinopathy (R3s)", the eye clinic must provide an appointment within 13 weeks. A symptomatic vision may threatens diabetic retinopathy, frequent dilated eye examinations are successful for the detection and monitoring of diabetic retinopathy (Cheung, 2010). In the early stages of illness, laser photocoagulation is good therapy. According to the Early Treatment Diabetic Retinopathy Study and Diabetic Retinopathy Research, patients who received treatment were 50% less likely to go blind from proliferative alterations and maculopathy (Porta, 2002; Lightman, 2003; Heng et al., 2013).

The World Health Organization (WHO) has defines quality of life as an individual's perceptions of their position in life, as well as their objectives, expectations, standards, and worries, in the context of the culture and value systems in which they live. The physical and mental components of health related quality of life (HRQOL) are severely harmed by the presence of DR and macular oedema, vision loss and comorbidities (Deswal et al., 2020). In persons having DR, several studies have shown both a quantitative and qualitative reduction in health related quality of life. In the past, several studies have recorded the development and psychometric properties of the Visual Function Questionnaire (VFQ-25). The VFQ-25 has been indicated to be superior to sharp sight in determining the vision related quality of life. It has been developed as an appropriate instrument to determine a patient's vision related quality of life and the treatment effects in DR. (Pereira DM et al., 2017). The Short Form 36 and the Sickness Impact Profile are some of the generic systemic instruments of quality of life that does not observed to correlate well with visual performance as ophthalmic measures. The newer Visual Function Questionnaire 25 (VFQ-25) and visual functioning 14 are applied to ophthalmic conditions but not applicable to non-ophthalmic conditions (Brown et al., 2002). Loss of vision due to DR and restrictions of movement has reduced many aspects of quality of life (Woodcock A et al., 2004).

6. Diagnosis

Based on evident haemorrhages, lipid exudates, cotton wool spots, micro aneurysm, and neovascularisation, DR is clinically diagnosed (Cohen, 2016). Laboratory levels of haemoglobin A1c (HbA1c) are critical in the long-term follow-up management of DR individuals. It is also very important to monitor other diabetes sequelae and should also include examination of kidney function, lipid profile, microalbuminuria, and peripheral nerve function evaluations and foot assessments (Hendrick, 2015). Ophthalmologists use "fluorescein angiography and optical coherence tomography (OCT)" to determine the permeability (leakage) and thickness of retinal blood vessels to diagnose DR. However, modern techniques are becoming more frequently used, including OCT angiography (Whitehead et al., 2018). Over the past three decades, improvements in colour vision, visual fields, contrast sensitivity and responses to electroretinography have been well reported. Technical improvements introduced the new imaging techniques to be used in retinal diseases in clinical practice and science (Cohen, 2016).

Recent advancements in imaging techniques include fundus photography and fluorescein angiography which is superior to that of ophthalmoscopy due to superior optics, improved fluorescein angiography contrast, confirmation of vascular leakage, new imaging methods- such as tomography of optical coherence and angiography of optical coherence tomography and the capability of the observer to analyse magnified images without the need of moving patients (Cohen, 2016; Kwan, 2019).

6.1. Fundus Photography

Fundus photography is a quick, non-invasive, well-tolerated, and widely available imaging technique that generates high-quality retinal images and is commonlyprovide the range of DR by clinical evaluation. Conventional Colour Fundus Photography (CFP), the primary tool for measuring the posterior pole for several years uses a classic fundus camera of magnification ×2.5 with a 30 ° field of view, although modern fundus cameras can capture retinal fields of view in a single image between 30 ° and 55 ° (Kwan, 2019). The ETDR (Early Treatment of Diabetic Retinopathy Study) classification system has long been considered the gold standard for DR staging (Early Treatment of Diabetic Retinopathy Study) that make use of seven colour fundus photography fields to measure vascular lesions, but currently, the "Internal Clinical Diabetic Retinopathy and Diabetic

Macular Oedema Severity Scale" is a simplified scale based on the 2001 ETDRS system that is more user-friendly for clinicians. According to the ETDRS system, steered images can be used to cover a larger area -of the retina, such as the optical disc, vascular arcades, optical disc, and temporal region of the macula, with a field of view of 75 degrees. Multiple steered images enable each area to be assessed on its own by a clinician or grader and then resultin an overall severity evaluation for each eye (Kwan, 2019;Tan et al., 2016).

6.2. Optical Coherence Tomography

A non-invasive and rapid imaging method in which light waves are used to provide 2 dimensional and cross-sectional images of the retina or macular anatomy in vivo is termed optical coherence tomography (OCT) (Hendrick, 2015; Kwan, 2019). This plays a very important role in the diagnosis and therapy of the diseases related to the retina of the eye as it produces high-resolution pictures of retinal structure that enable volumetric quantification of retinal and choroidal thickness and macular edema (Kwan, 2019; Tan et al., 2016). OCT serves to differentiate DME subtypes, detect the presence of macular traction, and localise to specific retinal layers in DME. It can also be used to know the presence of enhanced retinal thickness with low intraretinal reflectivity area in the outer retinal layers and loss of foveal depression in DME (Bandello et al., 2010; Kwan, 2019). OCT retinal inner layer disorganisation (DRIL) - a suggested biomarker is found to be correlated with visual acuity and can predict the potential vision changes in patients of DME. DRIL is characterised by the loss of boundaries on OCT which is measured as the transverse extent between the inner plexiform, ganglion cell and outer nuclear plexiform layers of the retina. Recent advancements have also made it possible to picture the choroid under the RPE, and research has shown that in different retinal disorders, the choroidal thickness can be of prognostic significance. Major OCT drawback includes the inability to offer detailed data as it only collects images at a single point in time, the inability to see vascular changes, and the requirement for subject fixation (Tan et al., 2016; Kwan, 2019).

6.3. Fluorescein Angiography

Fluorescein Angiography (FA) is a tool for analysing the retinal vasculature in vivo using a fluorescent dye to provide data on vessel permeability and vascular activity over time. Traditional FAs normally cover 30–55º of the retina whereas the standard fundus cameras can be directed to image various structures of the retina, the images are taken at various stages of the angiogram, significant information can be lost as a result of fluorescein's limited transit period (Tan et al., 2016; Kwan, 2019). Using dye leakage seen on FA, the site of the breakdown of vessel or neovascularization can be determined for targeted laser therapies. Furthermore, FA's dye allows better visibility of lesions like microaneurysms and non-perfusion areas, aiding DR staging and monitoring (Hendrick, 2015; Kwan, 2019). FA has several disadvantages, the most serious of which is that it is an invasive and time-consuming procedure. FA used the contrast dye which has the potential to cause nausea & vomiting, seizure, allergy, urticarial, and even death (Kwan, 2019).

6.4. Optical Coherence Tomography Angiography

OCT angiography (OCTA) is a new technique that enables quick imaging by advanced spectral domain or swept-source OCT devices (SSOCT) to analyse variations in reflectivity and phase shift from blood vessels in the retina creating microvascular flow maps, as well as visualization by observing the light emitted by red blood cells as they pass through the retina's vessels. So OCTA provides a distinctly detailed three-dimensional picture of the choroidal and retinal vasculature and data on vascular flow at a particular point. OCTA technique provides doctors to see the choroidal and retinal microvasculature without needing to administer fluorescein intravenously. OCTA has an advantage over FA because the OCTA tool does not use contrast dye as in FA, but provides similar details such as detailed area of microaneurysm and non-perfusion as in FA, and is better able to image neovascularization. (Tan et al., 2016; Kwan, 2019).

7. Treatment Strategies for Diabetic Retinopathy

Controlling glucose levels have shown a decrease in the development of DR. It was observed in a clinical trial that with median HbA_{1c} levels as 7.3% a reduction by 76% was in the development of diabetic retinopathy. It was also observed that control of blood pressure by usingbeta-blockers or angiotensin-converting enzyme inhibitors leads to a 34% reduction in the progression of diabetic retinopathy and a 47% reduction in the worsening of visual activity. For pregnant women, it is recommended that eye examination is important in every trimester and within the first year of postpartum (Klein, 1990; Rossino, 2019).

7.1. Nutraceuticals

The non-pharmacological approaches for the treatment of diabetic retinopathy include treatment with nutraceuticals. Nutraceutical was coined in 1989 by Dr. Stephen De Felice. They are food or part of food that provide health

and medical benefit by preventing a disease from occurring and alsohelp to manage the disease. They show anti-inflammatory properties by decreasing the effect of nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and antioxidant properties. They also reduce vascular changes, neurodegeneration, and oxidative stress (by increasing the effect of endogenous antioxidant enzymes) (Rossino, 2019). Nutraceuticals such as polyphenols, saponins, and carotenoids may have the potential to counteract pathological anomalies involved in DR such as oxidative stress, vascular changes, inflammation, neurodegeneration etc.

Polyphenols are present in plants and have antioxidant and antimicrobial properties so that they can protect the plant from UV rays. A Polyphenols-rich dietimproves glucose metabolism, reduces HBA1C and insulin resistance in type 2 DM (Cao et al., 2019). Polyphenols show antioxidant properties by decreasing the reactive oxygen species. Polyphenols have different classes based on the number of phenol rings -flavonoids (Catechin), stilbenoid (resveratrol) etc. Curcumin is a potent activator of Nrf2 and is obtained from turmeric roots. A high level of nuclear factor erythroid 2-related factor 2 (Nrf2) protects the retina in DM by monitoring the protective response to oxidative stress (Nabavi et al., 2016).

Saponins are protective against retinal damage induced by oxidative stress. It includes-Ginsenoside Rg1, Ginsenoside Rb1and Notoginsenoside R1. Ginsenoside Rg1 has an anti-apoptotic effect by decreasing the cell death of INL and GCL cells, it forbid the changes in the diabetic retina (Gao et al., 2020). Ginsenoside Rb1 hasan antioxidative property by activating the Nrf2 pathway and inducing antioxidant enzymes (Dong et al., 2019). Notoginsenoside R1 extracted from Panax notoginseng increases the level of PTEN-induced putative kinase protein 1 (PINK) on the outer membrane of damagedmitochondria and on the other side, PINK increases Parkin also. Increased Parkin exhibit the neuroprotective function also. Parkin evoke the ubiquitin chain formation on the proteins that are present on the outer membrane of mitochondria and autophagy receptor get replenished to form autophagosome by attaching to autophagophore and it further leads to selective degradation of mitochondria by autophagy and it is called Mitophagy (Zhou et al., 2019).

Carotenoids are obtained from plants, fungi, and algae. They are a group of lipophilic and organic pigments. Carotenoid to show the antioxidant, neuroprotective and anti-inflammatory properties andare classified into 2 types – Carotenes only have hydrogen and carbon (such as Torulene). Xanthophylls have hydrogen, carbon, and oxygen (such as Crocin, Lutein, Zeaxanthin). Carotenoids decrease the making of ROS (reactive oxygen species) and RNS (reactive nitrogen species) in the retina (Fathalipour et al., 2020)

Some other nutraceuticals that are reported to be beneficial includes the Taurine, Lisosan G, Fufang Xueshuantong etc. Lisosan Gis Obtained from Triticum aestivum and has antioxidant property so it helps in reducing retinal damage by reducing oxygen stress (Amato et al., 2018). Fufang Xueshuantong maintains haemodynamic, diminishes the oedema of the retina, and decreases retinal thickening by activating the PPAR signalling pathway (Fathalipouret al., 2021). Taurine was first obtained from bile by Friedrich Tiedemann and Leopold Gmelin. The deficiency of taurine leads to metabolic disorders or diabetic complications (Sak et al., 2019). Some of the nutraceuticals known to be beneficial in DR are mentioned in table 2 (Nimse, 2015; Ahmadinejad et al., 2017; Rossino, 2019).

Table 2: Various nutraceuticals that have shown potential in the treatment of diabetic retinopathy (Nimse, 2015; Ahmadinejad et al., 2017; Rossino, 2019).

Polyphenols	Rutin
	Quercetin
	Kaempferol
	Luteolin
	Hesperetin
	Catechin
	Eriodictyol
	Deguelin
	Curcumin
	Resveratrol
Saponins	Ginsenoside Rb1
	Ginsenoside Rg1
	Notoginsenoside R1
Carotenoids	Crocin
	Lutein
	Zeaxanthin
Other	K24
	Taurine
	Lisosan G
	Ginger
	Fufang Xueshuantong
	AKBA

7.2. Pharmacological Drugs

The various local ocular treatment includes pars plana vitrectomy and laser photocoagulation of the retina. The

pharmacological agents for the treatment include anti-VEGF agents, corticosteroids, and specific moieties which are involved in biochemical pathways (Kastelan et al., 2013). A complication of diabetic retinopathy is diabetic macular oedema, now which canbe treated with intravitreal anti-VEGF drug administration, photocoagulation and corticosteroids delivered intravitreally (placing the medicine in the vitreous cavity of the eye). Photocoagulation is used for the treatment of diabetic retinopathy as well as diabetic macular oedema as it prevents the loss of vision (Kastelan et al., 2013). It has been proved that using corticosteroids such as dexamethasone, fluocinolone, and triamcinolone along with laser photocoagulation can significantly have a positive impact on the vision. Slow-release preparations of the corticosteroids have been made in the form of implants for drugs such as fluocinolones and dexamethasone. Studies now are suggestive of ophthalmic solutions containing NSAIDs for treatment of diabetic retinopathy, having good tissue penetrative properties (Sahoo et al., 2015; Semeraro et al., 2015). In various trials, it was concluded that vision improvement was seen after 1-2 years of administering anti-VEGF agents such as ranibizumab, bevacizumab, and aflibercept (Wells et al., 2015; Wells et al., 2016). Mean visual acuity was noted after treatment with the previously discussed anti-VEGF agents for 2 years, it was observed that aflibercept was superior in treating visual loss as compared to bevacizumab but not with ranibizumab(Boyer et al., 2014; Campochiaro et al., 2019). In a study conducted by Dave V et al., it has been stated that developed folic acid-modified gold nanoparticles in the delivery of sorafenib tosylate for treating diabetic retinopathy, the formulation had a sustained drug release and target delivery. In the Dipyridamole Aspirin Microangiopathy of Diabetes Study, it was concluded that early-stage treatment of diabetic retinopathy with a 900mg/day dose of aspirin reduced retinal microaneurysm(Kim, 2010; Dave et al., 2020). Drugs used for the treatment of diabetic retinopathy and ongoing clinical trials on diabetic retinopathy are mentioned in table 3 & 4.

Table 3: Pharmacological agents for the treatment of Diabetic Retinopathy (Kastelan et al., 2013; Wells et al., 2016; Dave et al., 2020).

Class of Drugs	**Agents**	**Action**	**Target**
Anti-VEGF	Ranibizumab	Blockage of vascular permeability, VEGF mediated inflammation	VEGF
	Bevacizumab		
	Pegaptanib		
Vitamins	Ascorbic Acid	Antioxidant property	Oxidative Stress
	Alpha-tocopherol		
NSAIDs	Aspirin	Inhibiting the production of prostaglandins and proinflammatory mediators	COX
RAS Blockers	Enalapril	RAS mediated inflammation is blocked	RAS
	Candesartan		
	Losartan		
Corticosteroids	Fluocinolone acetonide	Blocking proinflammatory transcription factors	Glucocorticoid receptor
	Triamcinolone acetonide		
	Dexamethasone		
Inflammatory Molecule Blockade	Infliximab	Inhibition of TNF-α induced inflammation	TNF-α
	Etanercept		

Table 4: Description of ongoing clinical trials for diabetic retinopathy (www.clinicaltrials.gov.in).

Test Drug/ Intervention	**Standard Drug/ Intervention**	**Status**	**ClinicalTrials.gov Identifier**
Runcaciguat	Placebo	Phase-2	NCT04722991
Port Delivery System Filled Implants with Ranibizumab 100mg/mL	Intravitreal Injection of Ranibizumab 0.5mg	Phase-3	NCT04503551
Combined Antioxidant Treatment	Placebo	Phase-3	NCT03702374

Aflibercept Injection		Phase-4	NCT04708145
Finerenone	Placebo		NCT04795726
6mg Brolucizumab	Pan retinal photocoagulation laser	Phase-3	NCT04278417
Conbercept intravitreal injection	Pan-retinal photocoagulation		NCT02911311
160mg Fenofibrate	Placebo	Phase-3	NCT04661358
APX3330	Placebo	Phase-2	NCT04692688
Conbercept	Panretinal coagulation		NCT03863535
145mg Fenofibrate	Placebo	Phase-4	NCT03439345
4mg Melatonin		Phase-3	NCT03478306
Aflibercept	Targeted laser therapy	Phase-4	NCT02432547

Conclusion

Many of the pathological states identified in DR, such as oxidative stress, inflammation, neurodegeneration, and vascular lesions can be relieved by the administration of appropriate pharmacological drugs including nutraceuticals also. Laser photocoagulation, vitreoretinal surgery, or intravitreal injections of pharmacological drugs targeting VEGF are the most common treatments for DR. On the other hand, these treatments only work in advanced stages of DR, and are ineffective for a longer period, and have side effects also. Non- pharmacological treatments are increasingly being used to address these difficulties. Only a few clinical studies have looked into the use of nutraceuticals for the treatment of DR, with the majority of them focusing on carotenoids. However, several studies are animal-related. It appears that using nutraceuticals in early DR may prevent further progression and could be a promising therapy to be used in DR. Future research is needed to explore the use of nutraceuticals in early and advanced stage DR also.

Conflict of Interests

The authors declare no conflict of interest, financial or otherwise.

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Authorship Contribution

Rupinder Kaur, Suman Baishnab: Conceptualization conceived- and designed the manuscript.
Rupinder Kaur, Shareen Singh, Rithik, Kirti, Suman Baishnab: Wrote the manuscript.
Suman Baishnab: Visualization.
Rupinder Kaur, Shareen Singh, Suman Baishnab: Editing of the manuscript.
Rupinder Kaur: Critically reviewed the article.

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