EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 9
187-194
Year: 2018

DIABETIC RETINOPATHY: AN OVERVIEW AND ROLE OF HERBAL PLANTS

***N. Jayasree, V. Jayasankar Reddy, V. Silvia Sudharshini, Dharani Prasad**

Department of Pharmacology, Krishnateja Pharmacy College, Tirupati. 517506. Andhra Pradesh, India.

***Corresponding Author: N. Jayasree**
Department of Pharmacology, Krishnateja Pharmacy College, Tirupati. 517506. Andhra Pradesh, India.

Article Received on 01/07/2018 **Article Revised on 22/07/2018** **Article Accepted on 13/08/2018**

ABSTRACT

The main objective of this review is detailed with the Diabetic retinopathy (DR) origin, complications, current treatment and their side effects and role of herbal plants in the treatment of Diabetic retinopathy. DR is the progressive disorder of chronic hyperglycemia. It is a leading cause of vision loss among working class. It is a multifactorial disease and some of them implicated in the pathogenesis of DR are Vascular endothelial growth factor (VEGF), Tumour necrosis factor- α (TNF-α), Interleukin-1β(IL-1β), Polyol pathway, oxidative stress, Protein kinase C-β(PKC-β).Photocoagulation, vitrectomy, anti VEGF agents and some anti inflammatory agents are currently in use. In this review, various molecular mechanisms, current treatment and their complications, importance of herbal plants in the treatment of DR have been discussed.

KEYWORDS: Diabetic retinopathy, vascular endothelial growth factor, Fluorescein angiography, Optical coherence tomography, Laser treatment, vitrectomy, Anti-VEGF drugs.

Diabetes

As per World Health Organization, diabetes mellitus is considered as a metabolic disorder of multiple etiologies characterized by chronic blood glucose level with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1]

Classification of diabetes mellitus

Diabetes can be classified are as follows: 1.Type -1 diabetes: In this type, there is a destruction of β cells, leading to absolute insulin deficiency.2. Type-2 diabetes: It is caused due to progressive insulin secretory defect on the background of insulin resistance.3. Gestational diabetes: Diabetes detected during third trimester of pregnancy is not clearly manifested.4. Specific type of diabetes: Diabetes caused due to other factors, e.g.: monogenic diabetic syndrome (i.e. neonatal diabetes& maturity-onset diabetes of the young), exocrine pancreas disease (i.e. cystic fibrosis) and drug or chemical – induced diabetes (such as in the treatment of HIV/AIDS or after organ transplant).[2,3] The chronic uncontrolled diabetes leads to progressive development of specific complications, which include: Eye (retinopathy), Kidney (nephropathy), Nerve (neuropathy), Autonomic dysfunction, Heart (atherosclerosis etc.), Cerebrovascular disease.[1]

Diabetic Retinopathy (DR)

Diabetic Retinopathy (DR) is the most enervative microvasculature disorder of retina caused due to chronic hyperglycemic condition.[4] It is a leading cause of vision loss among working class. According to WHO, DR causes 5% blinds worldwide.[5] It is estimated that two-third of all type 2 and almost all type 1diabetic patients may develop DR over a period of 15-20 years.[6] It occurs when diabetes damages the microvasculature of the retina. DR can cause leakage of retinal blood vessels or hemorrhage, distorting vision. The advanced stage of DR is Proliferative Diabetic Retinopathy (PDR), in which formation of new abnormal blood vessels takes place on the retinal surface, leading to scarring and cell loss in the retina .It may lead to severe eye damage, if left untreated.[7]

Stages of DR

DR can be classified based on absence or presence of new abnormal blood vessels in retina. In Non-Proliferative DR, early signs like retinal hemorrhage, microaneurysms, and cotton wool spots were detected. In Proliferative DR, angiogenesis takes place, due to increased levels of VEGF & PKC-β. DR may progress through four stages: Mild, moderate, severe Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR).[8]

Figure 1: Normal retina **Diabetic retinopathy**

Major Risk Factors

Duration of diabetes, poorer glyceamic & blood pressure control, pregnancy, obesity and puberty are the major risk factors associated with DR.

Symptoms

Diabetic retinopathy has no early symptoms. You may have no pain and there is no change in your vision as damage begins inside your eyes. When symptoms may do occur, they may include: Blurred vision, Spots or dark strings, Poor color vision.[9]

Putative mechanisms involved in Diabetic Retinopathy

1. **Advanced glycated end products**

Advanced glycated end products (AGEs) are heterogeneous group of molecules which forms at a constant but slow rate in the normal body starting at the embryonic development and accumulate with time. But, their formation is markedly accelerated in diabetes because of availability of excess glucose.[10] AGEs are produced from non-enzymatic reaction of carbonyl group of a reducing sugar like glucose with proteins, lipids and nucleic acid amino groups through maillard reaction. AGEs interact with a variety of cell surface AGE binding receptors such as Receptor for Advanced glycated end products (RAGEs), leading to cellular activation and generation of reactive oxygen species, proinflammatory events.[11]

2**. Polyol pathway**

The polyol pathway is a two step metabolic pathway in which glucose is reduced to sorbitol using NADPH (nicotinamide adenine dinucleotide phosphate) as a cofactor by aldose reductase. The sorbitol is then converted to fructose by sorbitol dehydrogenase. Diabetes favors the formation of sorbitol. Since sorbitol is impermeable to cellular membrane, it gets accumulated within the cell This accumulated sorbitol is thought to have multiple damaging effects in retinal cells. In addition to this, the fructose obtained from polyol pathway is phosphorylated to fructose-3-phosphate which in turn can be degraded to 3-deoxyglucosone; both of them can result in the production of AGEs. NADPH & $NAD^+$is necessary cofactors in redox throughout the body. Increased polyol pathway cause lesser availability of cofactors for glutathione reductase to regenerate glutathione results in increased oxidative stress, which in turn damage retina.[12,13]

3. Oxidative stress

Reactive oxygen species (ROS) is a free radical (hydroxyl radical, superoxide anion, hydroperoxyl radicals and lipid peroxyl radicals) with unpaired electron that normally participates in redox mechanism of some body molecules. In general ROS maintain in equilibrium however it's over expression can lead to a process called oxidative stress. This oxidative stress play vital role in the pathogenesis of DR. The retina is more susceptible to oxidation because of high energy demands and exposure to light. When this balance is failed, ROS create retinal cell injury by interacting with cellular components.[14] The antioxidants (tocopherols, ascorbic acid, and glutathione) or enzymes involved in free radical scavenging such as catalase, peroxidase and superoxide dismutase are depleted in diabetic retina.[15,16]

4. Angiogenic factors in DR

i. Vascular endothelial growth factor (VEGF)

VEGF is a pro inflammatory molecule that plays a vital role in the proliferation of new blood vessels and cause increased vascular permeability. The normal function of VEGFs is formation of new blood vessels during embryonic development, new blood vessels after injury, muscle following exercise and new vessels to bypass blocked vessels. The expression of VEGF is accelerated in response to hypoxia by a variety of cytokines. VEGF inhibits apoptosis caused by tumor necrosis factor. Thus, VEGF has been implicated in the pathogenesis of diabetic retinopathy.[17]

ii. Protein Kinase C-beta (PKC-β)

Protein Kinase C is a family of 12 isoforms, in which β1/2 isoform appears to be closely associated with the development of diabetic retinopathy.[8] PKC is a part of serine/threonine Kinase that catalyzes phosphorylation of proteins involved in signal transduction. The novel PKC isoforms are up regulated by diacylglycerol (DAG), which inturn is enhanced by hyperglycemia of diabetes The PKC activation may cause basement membrane and extracellular matrix alterations within the retinal

vasculature .It also increases retinal vascular permeability and angiogenesis related to its action on VEGF.[19]

5. Inflammatory factors in DR

i. Tumor Necrosis Factor-α (TNF-α)

TNF- α is a pro inflammatory cytokine that have been found to be in the vitreous fluid of diabetic retina. It has been reported that there is a strong correlation between TNF-α plasma levels and severity of DR. Endothelial dysfunction was induced by high serum levels of TNF-α in DR. In extension to that, increased TNF-α level in diabetic plasma has been shown to induce leukocyte-endothelial cell adhesion. In vivo studies revealed that TNF-α enhances angiogenesis and is required for VEGF induced endothelial hyperpermeabilty.[20]

ii. Interleukins-1β (IL-1β)

Interleukin-1β is a pro inflammatory cytokine that has a role in retinal capillary endothelial cell death in diabetes via activation of Nuclear factor-kappa B(NF-kappa B).It has been reported that the expression of NF-Kappa B is the early event takes place in DR that is sustained by increased in the death of retinal capillary.[5,21]

6. Renin-Angiotensin- Aldosterone System (RAAS)

The Renin-Angiotensin-Aldosterone system (RAAS) plays a vital role in the regulation of blood pressure, glucose metabolism, electrolyte and fluid homeostasis. The Renin, angiotensin converting enzymes I &II (ACE I&II) and angiotensin receptors (Ang) has been reported to increase in the retina during PDR. Both ACE and Ang II increases the VEGF levels leading to abnormal retinal angiogenesis with increased risk of retinopathy and its progression.[22]

7. Miscellaneous factors

Hemodynamic changes, leukostasis, cyclo-oxygenase 2 (COX-2), and inducible nitric oxide synthase may also found to be implicate in the pathogenesis of DR.[4,23]

Diagnosis of Diabetic Retinopathy

Diabetic Retinopathy can be detected through a complete dilated eye exam. This allows the doctor to check for the following: Abnormal blood vessels, swelling of the macula, fatty deposits in the retina, Damage to nerve tissue, leaking of blood vessels (hemorrhage) in the vitreous fluid, Retinal detachment.

1. Fluorescein Angiography

Fluorescein angiography is a technique used for exploring retinal circulation and choroid using a fluorescent dye and a specialized angiographic camera. For this, first of all your eye will be dilated, your doctor takes pictures of the inside of your eyes. Then a sodium Fluorescein dye will be injected intravenously, usually through an antecubital vein with adequate speed to produce high contrast mages of the early phases of the angiogram. Immediately after injection, pictures of the retinal blood vessels are taken, as the dye reaches the eye.[24]

2. Optical Coherence Tomography (OCT)

Optical Coherence Tomography (OCT) is an imaging technique that uses coherent light to capture micrometer resolution, two and three dimensional images from within optical scattering media. It provides information about vitreoretinal relationships that can clearly detect only with OCT.[25]

Management of Diabetic Retinopathy

1. Laser Therapy

There are two types of laser treatment commonly used to treat diabetic eye diseases based on the severity.

Focal or Grid Laser Photocoagulation

Focal photocoagulation is used to seal specific leaking blood vessels in a particular area of retina, usually the macula. It mainly targets microaneurysms near the macula, reducing the plasma leakage responsible for intra retinal swelling. It is commonly used to treat Diabetic Macula Edema (DME). It was reported that focal photocoagulation reduces the risk of moderate vision loss by 50%-70% in patients having macula edema. Some of the complications associated with this treatment are possible transient initial decrease in central vision, permanent central scotoma from in advertent fovea burns etc.[26,27]

Pan-Retinal or Scatter Photocoagulation

The pan-retinal photocoagulation treatment is used to slowdown the new abnormal blood vessel growth that have developed over a wider area of the retina .In this method about 1,200-1,800 tiny laser burns are applied to the periphery of the retina .It is widely used to treat PDR. It was reported that this treatment reduces the risk of severe vision loss by 50% in patients with severe Diabetic Retinopathy.[28] The major complications associated with this treatment are transient central vision loss from macular edema, vitreous hemorrhage if angiogenesis is present ,papillary dilation.[29]

Laser Photocoagulation will just slow down the progression of disease, it will not restore vision that has been already lost to disease, and it is not a cure. Patients need additional treatments.[30]

2. Vitrectomy

Vitrectomy is a surgical procedure where the vitreous humor that fills the eye cavity is removed. This includes removal of scar tissues, treatment of macular holes. Once surgery is completed, saline, gas bubbles or silicone oil may be injected into the vitreous gel to hold the retina in position. The main side effects associated with this treatment are vision loss, retinal detachment, cataract etc.[31]

3. Pharmacotherapy

Intravitreal Anti-inflammatory agents (corticosteroids)

Triamcinolone acetonide is a potent anti-inflammatory agent that has shown better improvement in DME and Age related macular degeneration. Fluocinolone acetonide got FDA approval for chronic, non infectious Uveitis treatment. Ozurdex® is a biodegradable dexamethasone that has been recently approved by the FDA for macular edema secondary to retinal vein occlusions. These intravitreal injections have shown evidence based clinical benefits in the treatment of DR & DME. Nepafenac, Etanercept, Infliximab are also FDA approved intravitreal injections for DME. Cataract and elevation of intra ocular pressure are serious side effects associated with this therapy.[32,33]

Anti VEGF drugs

Intravitreal Bevaciumab (Avastin) and Ranibizumab are used as clinical adjunct to pan-retinal photocoagulation. VEGF Trap Eye (Aflibercept, EYLEA®) is a recombinant fusion protein waiting for its approval from FDA. JSM6427, TG100801, ATG3 are in clinical trials. At present these VEGF inhibitors are getting popularity in DR treatment However, these intravitreal Anti VEGF drugs have also serious side effect like retinal detachment.[32,33]

Vitreolytic agents

Vitrase (Hyalurodinase ovine) which is FDA approved as a spreading agent, is the first and pure, preservative free, thimerosal free, ovine hyaluronidase. Intravitreal Vitrase has shown efficacy and safety in phase 4 clinical trial to investigate its promotion of the clearance of vitreous hemorrhage from PDR, although this purpose is not FDA approved.[32,33]

Role of Herbal Plants on Diabetic Retinopathy

Curcumin

Curcuma longa (turmeric) is a common spice used in Indian cuisine. Curcumin (1, 7-bis (4-hydroxy 3-methoxyphenyl)-1-6, heptadiene -3, 5-dione) is also known as diferuloylmethane. It is the natural polyphenol found in the rhizome of *curcuma longa*. It's been used traditionally in Asia for its antimicrobial, antimutagenic, anticancer properties. S. k. Gupta *et al.,* investigated the prevention of STZ induced diabetic retinopathy in wistar albino rats when treatment of oral Curcumin (1g/kg) was given and accomplished out for a period of 16 weeks. The rats were analyzed for hyperglycemic, antioxidant, and inflammatory parameters. Transmission electron microscopy for the evaluation of histological changes. However, Curcumin treated rats showed positive modulation of antioxidant system and also prevented proinflammatory cytokines, vascular endothelial growth factor, tumor necrosis factor α. Curcumin treated diabetic rats also showed defense against degeneration of endothelial cell organelles and increase in basement membrane thickness.[34] Jayant *et al.,* studied the protective effects of curcuminoids from regular (RC) and soluble (SC) Curcumin. Treatment with SC and RC prevented loss of rhodopsin protein expression (RHO) and nerve growth factor (NGF) and prevention of hypoxia in retinas by decrease in the hypoxia-inducible factor 1-alpha (HIF-1α).On the contrary, SC reduced the VEGF expression and prevented the drastic increase in the mRNA levels of Glial fibrillary acidic protein (GFAP) but no effect of RC treatment was seen.[35]

Quercetin

Quercetin (Qctn) is a flavanol that is presented predominant in fruits, vegetables, and tea. It is a promising food component, which can prevent lifestyle related diseases. Red leaf lettuce, onion, and green tea have huge amount of quercetin. The anti-inflammatory, antioxidant, and other molecular mechanisms may prevent lifestyle related diseases. The utilization of intake of quercetin containing rich diet attenuated STZ-induced diabetic symptoms in mice. Qctn also allayed obesity, hyperglycemia, hyperinsulinemia and dyslipidemia in (57BL/6J) mice provided a western diet rich in fat, sucrose and cholesterol. Binit Kumar *et al.*, reported the neuroprotective effects of quercetin in STZ induced diabetic rats, on retinal oxidative stress, apoptosis, and neuroinflammation. Diabetic rats are given Qctn (25 and 50mg/kg) orally for six months and were assessed for antioxidant and inflammatory, nuclear factor kappa B (NF-KB), caspase-3, Glial fibrillary acidic protein (GFAP) and aqauaporin-4(AQP4) expressions and any changes are evaluated by light microscopy. The results suggested that Qctn treated rats restored their glutathione levels and antioxidant enzyme levels compared to diabetic rats. Also, lower levels of cytokines (TNF α and IL-β) were seen compared to diabetic retinae. As per the changes in the light microscopy, the protective effects of Qctn on NF-KB and inhibitory caspase-3 expression. Qctn also inhibited the hyperglycemia induced increases in GFAP and AQP4 expressions compared with untreated diabetic retinae.[36]

Litsea japonica

Litsea japonica (Thumb) is a Korean native belonging to the family (Lauraceae) which is the common vegetable food in Korea. Chemical constituents include essential oils, lactones, alkaloids, and terpinoids. Kim *et al.*, investigated the ability of ethanolic extract of L. japonica as a prevention of retinal leakages in type II db/db mice. *L. japonica* extract (LJE) at a dose of 100,250mg/kg were given once daily for 12 weeks. Treatment with LJE blocked hyperglycemia induced blood retinal barrier breakdown and decreased retinal VEGF expression in db/db mice. It also inhibited occludine degradation a tight junction protein.[37] Kim *et al.,* also evaluated the protective effect of L. japonica extract on diabetes induced lens opacification and its protective mechanisms in db/db mice. The diabetic mice were treated with LJE at a dose of 100 and 250 mg/kg once daily for 12 weeks. An in vitro study reveals its dose dependent inhibition of aldose reductase in rat's lens. In extension to this, LJE

inhibits lenticular sorbitol accumulation and lens architectural changes induced by hyperglycemia.[38]

Hesperetin

The most habitual flavonoids found in citrus fruits are Hesperetin. It has been widely studied for its anticancer and hypolipidemic potential. Hesperetin also possess retinal vasculoprotective property. Binit Kumar *et al.*, studied the effects of Hesperetin on diabetes induced retinal oxidative stress, neuro inflammation and apoptosis in rats. The STZ induced diabetic rats received Hesperetin treatment (100mg/kg) and continued to 24 weeks and were evaluated for antioxidant(SOD, CAT, GSH) inflammatory cytokines (TNF-α, IL-1β), caspase-3, GFAP and AQP4expressions.Light microscopy and transmission electron microscopy (LM,TEM) were used to study histological changes. Results indicate that the Hesperetin treated rats showed increase in GSH levels and lower levels of cytokines compared to diabetic retinae. It also diminished the expression of caspase-3, GFAP, and AQP4. Protective effects on Muller cell process and photoreceptors as seen in LM images and relatively thin basement membrane in TEM study were recorded in Hesperetin treated diabetic retina.[39]

Trigonella foenum-graecum

Commonly known as fenugreek pertaining to the family (Leguminosae) utilized as a spice in India. The principal active constituents are 4-hydroxy isoleucine &trigonelline. It also possesses notable content of saponins, a fiber and an alkaloid. *Trigonella foenum-graecum* is prominently known to be antidiabetic.[40] The protective effects of fenugreek in STZ induced diabetic rat retina were found, when the fenugreek treatment (100 and 200mg/kg) was given and continued to 24 weeks and assessed for inflammatory, angiogenic and antioxidant parameters done by S.K Gupta *et al.,*. Retinal vascular leakage diagnosed by Fluorescein angiography and basement membrane thickness by electron microscopy. It results in marked reduction in the expression of inflammatory and angiogenic molecular biomarkers in fenugreek treated rats. It shows lesser thickening of basement membrane and no vascular leakage in fenugreek treated rats compared with diabetic rats.[41]

Moringa oleifera

Moringa oleifera (MO) commonly called drumstick or horse radish is a widely known nutritious plant belonging to the family Moringaceae. It is prominent to the Asian people (India, Pakistan). The leaves of MO contain a rich source of β carotene, protein, minerals and flavonoids (gelatin, rutin, quercetin, beta-sitosterol, caffeoylquinic acid and kaempferol). The various biological activities reported are hypoglycemic, anti-inflammatory, antioxidant, anti cancer and antimicrobial properties.[42] The aqueous leaf extract of MO 100 mg/ kg were given to the diabetic rats priorly induced with STZ for 24 weeks, and were measured for inflammatory, angiogenic, antioxidant parameters, fluorescein angiography were taken to check retina vascular leakage. The results represent that MO showed expressive inhibition in inflammatory and angiogenic parameters. The MO treated retinae showed inhibition in the dilation of retinal blood vessels. Fluorescein angiography of diabetic retinae treated with MO showed unflawed retinal vasculature, decrease in thickening of basement membrane was seen in MO treated diabetic retinae performed by transmission electron microscopy.[43]

Tinospora cordifolia

Tinospor acordifolia (Guduchi) belongs to the family Menispermaceae, has been used in Ayurveda from decades. The various biological activities of *Tinospora cordifolia* (TC) are liver protective, cholesterol lowering and anticancer.[44] TC also lowers some of the diabetic complications like healing of diabetic foot ulcers and diabetic cataract. S.S. Agrawal *et al*, studied the management of diabetic retinopathy in STZ induced rats by TC. The diabetic rats treated with TC (250mg/kg) were evaluated for lenticular and fundus changes, biochemical, histopathological, angiogenic and anti-inflammatory parameters. According to the results, decrease in blood glucose in TC treated rats and prevention of cataract development was seen. It significantly showed inhibition in Angiogenic (VEGF and PKC), lowering of TNF α and IL-1β levels. It also restored the levels of antioxidant enzymes (GSH and CAT). Thinning of basement membrane in TC treated rats was seen.[45]

Green tea

Camellia sinensis (green tea) is one of the extensive beverages in Asia having a traditional medicinal value. It is widely known for its anti-inflammatory, antioxidative, antiarthritic, antiviral, neuroprotective and anticarcinogenic properties.[46] Binit Kumar *et al.*, has been studied its effect on diabetes induced retinal oxidative stress and pro inflammatory parameters. The STZ induced diabetic rats were treated with GT (200mg/kg) for 16 weeks and are assessed for glyceamic, anti-inflammatory and antioxidant parameters. TEM is used to evaluate histological changes. However, GT treated rats showed marked GSH, SOD, CAT levels restoration than that of diabetic rats. The expression of inflammatory parameters in GT treated retinae was inhibited. GT also demolished the thickening of retinal capillary basement membrane.[47]

Ocimum sanctum

Ocimum sanctum Linn (Lamiaceae) is a tropical weed which is eminent and adored by Hindu religion. Studies revealed that the levels of blood glucose were reduced by *Ocimum sanctum* (Tulsi).[48] The main active constituent present in Ocimum is eugenol. Halim *et al.*, investigated the antidiabetic retinopathy activity of aqueous extract of tulsi with vitamin E. Diabetes was induced by Streptozotocin (STZ) IP injection 60mg/kg in citrate buffer (P^H 6.3) and left to a period of one month to see the changes in the retina and confirmed as diabetic retinopathy. The treatment of ocimum (250mg/kg) along

with vitamin E (544mg/kg) was given to the diabetic rats for 16 weeks and were tested for biochemical parameters and retinal changes. The results suggest that ocimum along with vitamin E significantly reduced the plasma levels of glucose, HbA_{1c}, improved lipid profile and elevated the antioxidant enzymes. Fluorescein angiography of combined treated diabetic rats showed remarkable improvements.[49]

Azadiracta Indica

Azadiracta indica (neem) is a well-known medicinal plant, used in Ayurveda for treating various diseases. It belongs to Meliaceae family. It is indigenous to India and is also found in some other Asian countries. The active chemical constituents of neem includes diterpenes (sugiol & nimbiol), triterpenes (β-sitosterol & stigmasterol), tetraterpenoids (azadiractin-k), limonoids, flavanol glycosides (quercetin, myricetin) etc.[50] It has been reported to possess cardiovascular, immunomodulatory, hypoglycemic and a number of other effects.[51] Halim Eshrat M. Ali Husain investigated the effect of aqueous leaf extract of *Azadiracta Indica* in STZ induced DR in rats. The diabetic rats were treated with aqueous extract of neem at a dose of 250mg/kg b. w for 16 weeks. The Anti-diabetic Retinopathy activity was evaluated by Fluorescein angiography, glyceamic parameters and lipid profile. It results in gradual but significant reduce in the blood glucose levels &shows better improvement in serum total, LDL, HDL cholesterol and triglycerides which increased during diabetes in rats. It also reversed DR.[52]

CONCLUSION

Based on WHO, over 171 million people were suffered from diabetes in 2000.It is estimated that this number will increase to more than 366 million by 2030.Diabetic retinopathy is one of the most dangerous blind causing disease caused due to various pathological factors. The exact mechanism by which the disease occurs may not clearly known. The current treatments available are anti VEGF drugs, vitrectomy, photocoagulation, but these treatments lead to severe side effects and intolerable to patients. The clinical diagnostic procedure for DR is also complex and costly. Despite to this, many studies have been shown that herbal plants are very effective in the prevention and treatment of DR. Hence there is a need to initiate these herbal drugs into clinical therapies to manage diabetic retinopathy with lesser or no side effects.

REFERENCES

1. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. World health organization. Department of Non communicable disease surveillance. Geneva, 1999; 2-3.
2. Habtamu Wondifraw Baynest. Cassification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. Journal of Diabetes & Metabolism, 2015; 6(5): 1-9.
3. American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care, 2015; 38(sup 1): S8-S16.
4. Ankur Rohilla, Rupesh kumar, Seema Rohilla, Ashok kushnoor. Diabetic Retinopathy: Origin and Complications. European Journal of Experimental Biology, 2012; 2(1): 88-94.
5. Anand Kumar Gond, SK. Gupta. Diabetic Retinopathy: Role of Traditional Medicinal plants in its management and their Molecular Mechanisms. International Journal of Pharmaceutical science invention, 2017; 6(6): 1-14.
6. Salil S Gadkari, Quresh B Maskati, Barun kumar Nayak. Prevalence of Diabetic Retinopathy in India: The All India Ophthalmological society Diabetic Retinopathy eye screening study 2014. Indian journal of Ophthalmology, 2016; 649(1): 38-44.
7. Diabetic Retinopathy, What you should know. U.S. Department of Health and Human Services. National Institute of Health. National Eye Institute, 1-15. www.nei.nih.gov.
8. Faruque D Ghanchi, Paul M Dondson, Usha Chakravarthy, Jon Gibson, The Royal College of Ophthalmologists clinical guidelines for diabetic retinopathy: A Summary. Eye, 2013; 1-143.
9. Diabetic Eye Disease-National Institute of Diabetes and Digestive and Kidney Diseases, 2017; https://www.niddk.nih.gov.
10. Melpomeni Peppa, Jaime Uribarri, Helen Vlassara. Glucose, Advanced Glycated End Products, and Diabetic Complications: What is New and What Works American Diabetic Association. Clinical Diabetes, 2003; 21(4): 186-187.
11. Yashodhara Sharma, Sandeep Saxena, Arvind Mishra, Anitha Saxena, Shankar Madhav Natu. Advanced glycated end products and diabetic retinopathy. Journal of Ocular Biology, Diseases and Informatics, 2012; 5(3-4): 63-69.
12. Mara Lorenzi. The polyol pathway as a mechanism for diabetic retinopathy: Attractive, Elusive and Resilient. Experimental Diabetes Research, 2007; 1-10.
13. K.H. Gabbay. Hyperglycemia, polyol metabolism, and complications of diabetes mellitus. Annual Review of Medicine, 1975; 26: 521-536.
14. G D Calderon, O H Juarez, G E Hernandez, S M Punzo, ZD De la Cruz. Oxidative stress and diabetic retinopathy: development and treatment. Eye, 2017; 31: 1122-1130.
15. Milam A Brantley, Paul Sternberg. Mechanisms of Oxidative Stress in Retinal Injury (chap 22). Retina (fifth edition), 2013; 1: 517-528.
16. Francois Gagne. Oxidative stress (chap 6). Biochemical Ecotoxicology, 2014: 103-115.
17. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z, Vascular endothelial growth factor (VEGF) and its receptors. The FASEB journal, 1999; 13(1): 9-22.

18. Daisuke Koya, George L.King. Protein Kinase C Activation and the Development of Diabetic Complications. Diabetes, 1998; 47: 859-866.
19. Manvi Prakash, Jennifer K.Sun, George L.King. The Role of Protein Kinase C in Diabetic Retinopathy. In: Duh E.J. (eds) Diabetic Retinopathy, 2008; 207-216.
20. Ahmed M. Abu El-Asrar. Role of inflammation in pathogenesis of diabetic retinopathy. Middle East African Journal of Ophthalmology, 2012; 19(1): 70-74.
21. R A Kowluru, S Odenbach. Role of Interleukin 1β in the pathogenesis of Diabetic retinopathy. British Journal of Ophthalmology, 2004; 88(10): 1343-1347.
22. Zohreh Rahimi, Mahmodreza Moradi, Hamid Nasri. A systemic review of the role of renin-angiotensin aldosterone system genes in Diabetes Mellitus, Diabetic Retinopathy and Diabetic Neuropathy. Journal of Research in Medical Sciences, 2014; 19(11): 1090-1098.
23. Zoanna M.Tarr, Kirti Kaul, Mohit Chopra, Eva M Kohner, Rakesh Chibber. Pathophysiology of Diabetic Retinopathy. ISRN Opthalmaology, 2013; 1-13.
24. Debra Sullivan. Fluorescein Angiography. Healthline, 2016. https://www.healthline.com.
25. Lang G.E. Optical coherence Tomography findings in Diabetic Retinopathy. Diabetic Retinopathy, 2007; 39: 31-47.
26. Early Treatment Diabetic Retinopathy Study Research group. Early photocoagulation for Diabetic Retinopathy. ETDRS report number 9. Ophthalmology, 1991; 98: 766-785.
27. Laser photocoagulation for Diabetic retinopathy. WebMD. https://www.webmd.com.
28. Marilyn Haddrill. Treatment of Diabetic Retinopathy and Macular Edema. All about vision. https://www.allaboutvision.com.
29. Laser photocoagulation. Docshop.com, 2017. https://www.docshop.com.
30. Ryan J.fante, Vikram D. Durairaj, Scott C.N. Oliver. Diabetic retinopathy: An update on Treatment, The American Journal of Medicine, 2010; 123(3): 213-216.
31. Vitrectomy. American society of retina specialist. https://www.asrs.org/patients/retinal-diseases/25/vitrectomy.
32. B kumar, S K Gupta, R Saxena, S Srivastava. Current trends in the pharmacotherapy of Diabetic Retinopathy. Journal of Post graduate Medicine, 2012; 58(2): 132-139.
33. Lei Lu Ying Jiang, Ravindran Jagannathan, Yanli Hao. Current Advances in Pharmacotherapy and Technology for Diabetic Retinopathy: A systemic Review. Journal of Opthalmology, 2018; 1-13.
34. Suresh Kumar Gupta, Binit Kumar, Tapas Chandra Nag, Shyam Sunder Agrawal, Renu Agrawal, Puneet Agrawal, Rohit Saxena, Sushma Srivastava. Curcumin Prevents Experimental Diabetic Retinopathy in Rats Through Its Hypoglycemic, Antioxidant, and Anti –Infammatory Mechanisms, 2011; 27(2): 123-130.
35. Jayant Deshpande, Shanarnarayanan Jeykodi, Bhanupraash Reddy G, Sreenivasa Reddy, Vijaya Juturu. Soluble Curcumin in the Prevention of Diabetic Retinopathy via Modulation of Anti-Oxidant Activity and Genetic Pathways-In Vivo Model. Advances in Ophthalmology & Visual System, 2015; 3(1): 1-8.
36. Binit Kumar, Suresh Kumar Gupta, Tapas Chandra Nag, Sushma Srivastava, Rohit Saxena, Kumar Abhiram Jha, Bharthu Parthasarthy Srinivasan. Retinal neuroprotective effects of quercetin in Streptozotocin-induced diabetic rats. Experimental Eye Research, 2014; 125: 193-202.
37. Junghyun Kim, Chan-sik kim, IK Soo Lee, Yun Mi Lee, Eunjin Sohn, Kyuhyung Jo, Joo Hwan Kim, Jin Sook kim Extract of Litsea japonica ameliorates blood -retinal barrier breakdown in db/db mice. Endocrine, 2013.
38. Junghyun Kim, Chan-sik kim, Eunjin Sohn, Yun Mi Lee, Kyuhyung Jo, Jin Sook kim . *Litsea japonica* Extract Inhibits Aldose Reductase Activity and Hyperglycemia-Induced enticular Sorbitol Accumulation in db/db Mice. Evidence-Based Complementary and Alternative Medicine, 2015; 1-5.
39. Binit Kumar, Suresh Kumar Gupta, B. P. Srinivasan, Tapas Chandra Nag,, Sushma Srivastava, Rohit Saxena, Kumar Abhiram Jha. Hesperetin rescues retinal oxidative stress, neuroinflammation and apoptosis in diabetic rats Microvascular Research, 2013; 87: 65-74.
40. Renuka C, Ramesh N, Saravanan K. Evaluation of the antidiabetic effect of *Trigonea foenum-graecum* seed powder on alloxan induced diabetic albino rats. International Journal of Pharm Tech Research, 2009; 1(4): 1580-1584.
41. Suresh Kumar Gupta, Binit Kumar, Tapas Chandra Nag, B.P. Srinivasan, Sushma Srivastava, Shrikant Gaur, Rohit Saxena. Effects of *Trigonella foenum-graecum* (L.) on retinal oxidative stress, and proinflammatory and angiogenic molecular biomarkers in Streptozotocin-induced diabetic rats. Mol. Cell Biochem, 2014; 388: 1-9.
42. Lakshmipriya Gopalakrishnan, Kruti Doriya, Devarai Santhosh kumar. *Moringa oleifera*: A review on nutritive importance and its application. Food Science and Human Wellness, 2016; 5(2): 49-56.
43. Suresh Kumar Gupta, Binit Kumar, B.P. Srinivasan, Tapas Chandra Nag, Sushma Srivastava Rohit Saxena, Ashutosh Aggarwal. Retinoprotective Effects of *Moringa oleifera* via Antioxidant, Anti-Inflammatory and Anti-Angiogenic Mechanisms in Streptozotocin-Induced Diabetic Rats. Journal of Ocular Pharmacology and Therapeutics, 2013; 29(4): 419-426.

44. Soham Saha, Shyamasree Ghosh. *Tinospora Cordifolia*: One pant, many roles. Ancient Science of life, 2012; 31(4): 151-159.
45. Shyam S. Agrawal, Salma Naqvi, Suresh K. Gupta, Sushma Srivastava. Prevention and management of diabetic retinopathy in STZ diabetic rats by *Tinospora Cordifolia* and its molecular mechanisms. Food and Chemical Toxicology, 2012; 50: 3126-3132.
46. Sabu M Chacko, Priya T Thambi, Ramadasan Kuttan, Ikuo Nishigaki. Beneficial effects of green tea: A literature review. Chinese Medicine, 2010; 5(13): 1-9.
47. Binit Kumar, Suresh Kumar Gupta, Tapas Chandra Nag, Sushma Srivastava, Rohit Saxena. Green Tea Prevents Hyperglycemia-Induced Retinal Oxidative Stress and Inflammation in Streptozotocin Induced Diabetic Rats; Ophthalmic Research, 2011; 47: 103-108.
48. Eshrat Halim M. A. Hussain, Kaiser Jami, Mala Rao. Hypoglycaemic, hypolipidemic and antioxidant properties of tulsi *(Ocimum sanctum linn*) on Streptozotocin induced diabetes in rats. Indian Journal of Clinical Biochemistry, 2001; 16(2): 190-194.
49. Halim Eshrat M, A. K. Mukhopadhyay. Effect of *Ocimum sanctum* (Tulsi) and vitamin E on Biochemical parameters and Retinopathy in Streptozotocin induced Diabetic rats. Indian Journal of Clinical Biochemistry, 2006; 21(2): 181-188.
50. Kokate, C. K, A.P. Purohit, S. B. Gokhale. Drugs Containing Glycosides. In: Pharmacognosy, Kokate, C.K, A. P. Purohit, (36th Ed): 233-234.
51. Chhibber S, Sharma N. Medicinal and Therapeutical Potential of Neem (*Azadiracta indica*): A Review. International Journal of Scientific and Research Publications, 2014; 4(5): 1-5.
52. Halim Eshrat M. Ali Hussain. Reversal of Diabetic Retinopathy in Streptozotocin induced Diabetic Rats Using Traditional Indian Anti-Diabetic plant, *Azadirachta indica* (L). Indian Journal of Clinical Biochemistry, 2002; 17(2): 115-123.