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Review Article

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SYNTHETIC AND HERBAL APPROCHES FOR THE TREATMENT OF DIABETIC RETINOPATHY

Patle R. R.*, Nandgaye D. C., Fulwar R. D., Udapure H. N., Harinkhede A. G., Pande S. K., Rane P. T. and Kapgate K. S.

Chhatrapati Shivaji College of Pharmacy, Deori, Dist-Gondia. 441902.

***Corresponding Author: Patle R. R.**

Chhatrapati Shivaji College of Pharmacy, Deori, Dist-Gondia. 441902.

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ABSTRACT

Diabetes mellitus is a metabolic abnormality in which there is a failure to utilise glucose and hence a state of hyperglycaemia can occur. Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus, leading to vision loss and blindness. Hyperglycemia-induced oxidative stress and inflammation contribute to DR pathogenesis. This review discusses the stages of DR, including non-proliferative and proliferative forms, and highlights the importance of early detection and timely intervention. This review compares synthetic drugs (bevacizumab, ranibizumab, aflibercept, brolucizumab, faricimab) and natural products (turmeric, tulsi, moringaoleifera, fenugreek, green tea) in DR treatment. Synthetic drugs target vascular endothelial growth factor (VEGF) and angiogenesis, while natural products exhibit antioxidant, anti-inflammatory, and hypoglycemic properties. Studies demonstrate efficacy of both approaches, but natural products offer potential advantages, including: Multi-target mechanisms, Lower risk of adverse effects, Cost-effectiveness, Enhanced bioavailability.

KEYWORD: Diabetic Retinopathy, Synthetic Drugs, Herbal Drugs**,** Anti-VEGF.

INTRODUCTION

Diabetes mellitus is a metabolic abnormality in which there is a failure to utilise glucose and hence a state of hyperglycaemia can occur. If hyperglycaemia continues uncontrolled over time, it will lead to significant and widespread pathological changes, including involvement of the retina, brain and kidney.[1]

Diabetic retinopathy (DR) is a microvascular disorder occurring due to the long-term effects of diabetes mellitus. Diabetic retinopathy may lead to vision-threatening damage to the retina, eventually leading to blindness. It is the most common cause of severe vision loss in adults of working age groups in the western world.[2] Early detection and timely intervention are the keys to avoiding blindness due to diabetic retinopathy. The number of patients with diabetic retinopathy in America is estimated to reach 16.0 million by 2050, with vision-threatening complications affecting around 3.4 million of them.[3] The usefulness of strict glycemic control was clearly seen in clinical trials like the UK Prospective Diabetes Study (UKPDS) and Diabetes Control and Complication Trial (DCCT).[4][5]

Uncontrolled diabetes can lead to many ocular disorders like cataracts, glaucoma, ocular surface disorders, recurrent stye, non-arteritic anterior ischemic optic neuropathy, diabetic papillopathy, and diabetic retinopathy. Diabetic retinopathy may lead to vision-threatening damage to the retina, eventually leading to blindness; it is the most common and severe ocular complication.[6][7][8] Poor glycemic control, uncontrolled hypertension, dyslipidemia, nephropathy, male sex, and obesity are associated with worsening diabetic retinopathy.[9][10] Typical fundus features of diabetic retinopathy include microaneurysms, hard exudates, macular edema (diabetic macular edema or DME), and new vessels (in proliferative DR or PDR). The management options include strict control of the systemic conditions, intravitreal pharmacotherapy, and laser photocoagulation. With early diagnosis and prompt management, good final visual acuity may be achieved in most patients with DR.

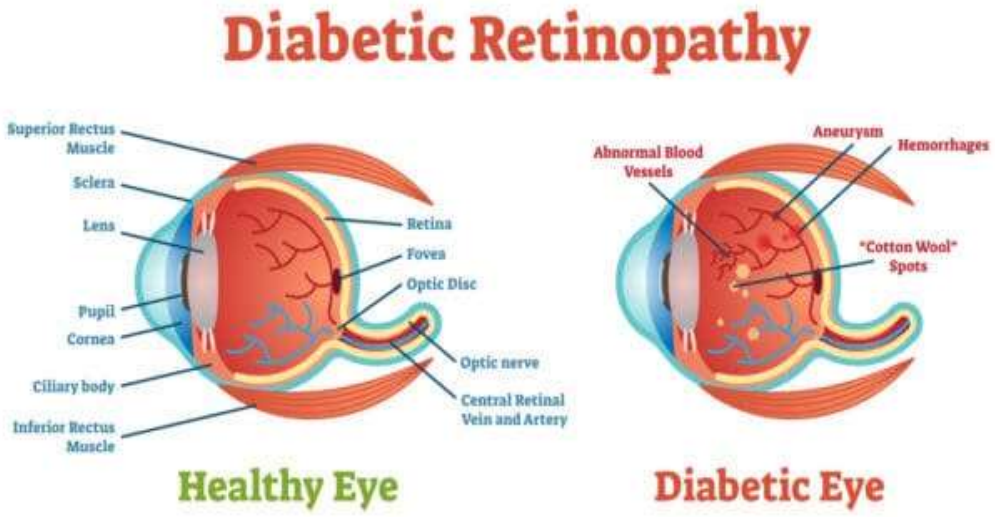

Fig. 1: Diagrammatic representation of healthy retina and diabetic retinopathy.

Types of Diabetic Retinopathy (DR)

1. Non-Proliferative diabetic retinopathy

- **No Retinopathy:** No retinal lesions
- **Very Mild NPDR:** Micro aneurysms only
- **Mild NPDR:** A few micro aneurysms, retinal hemorrhages & hard exudates
- **Moderate NPDR:** Retinal hemorrhages (about 20 medium-large per quadrant) in 1-3 quadrant + cotton wool spots (between the grades mild and severe NPDR)[11][12]

2. Proliferative diabetic retinopathy

- **Mild to moderate PDR-** NVD or NVE insufficient to meet high-risk characteristics
- **High-Risk PDR**
  - NVD greater than ETDRS standard photograph 10A (about 1/3 disc area).
  - Any NVD with vitreous hemorrhage.
  - NVE greater than 1/2 disc area with vitreous hemorrhage.

Etiology[13]

Diabetic retinopathy affects people with diagnosed or undiagnosed diabetes mellitus. The propensity to develop diabetic retinopathy is directly proportional to the patient's age and duration of diabetes, as well as poor glycemic control and fluctuating blood pressure levels.

Risk factors for diabetic retinopathy[14]

- Non-modifiable
  - Puberty
  - Pregnancy
- Modifiable
  - Hypertension
  - Obesity
  - Dyslipidemia
  - Poor glycemic control
  - Nephropathy
- Newer risk factors
  - Inflammation
  - Apolipoprotein
  - Hormonal influence - leptin and adiponectin
  - Vitamin D
  - Oxidative stress
  - Genetic factors

Symptoms

You might not have symptoms in the early stages of diabetic retinopathy. As the condition progresses, you might develop:

- Spots or dark strings floating in your vision (floaters)
- Blurred vision
- Fluctuating vision
- Dark or empty areas in your vision
- Vision loss
- Poor night vision

Pathophysiology

Diabetic retinopathy is a microvascular disease, characterized in various ways based on elevated vascular flow and vascular leakage due to the presence of vascular lesions, cell inflammation, edema in tissues, adhesion molecule expression and cytokines, reactive glia, apoptosis of inner retinal cell, and neovascularization. BRB impairment thickens the retina, as well as increasing leukocytosis, which is an intravascular immune response and one of the early clinically recognizable pathologies of DR. It causes the adherence of white blood cells (WBCs) to the endothelial cells lining the blood vessels that influence the plugging of capillaries and vascular leakage.[15] In the pathogenesis of DR, hyperglycemia plays an important role. The biochemical pathways associated with hyperglycemia-induced vascular damage include elevated glucose flux by means of the polyol pathway, AGE-product

accumulation, inflammation, as well as the activation of protein kinase C (hexosamine pathway).[16],[17] The overabundance of superoxide in the mitochondria induced by hyperglycemia leads to oxidative stress, which acts as a stressor, linking all these metabolic pathways. Oxidative stress gives rise to multiple early clinical hallmarks of DR that include a thickened basement membrane, pericyte apoptosis, and mitochondrial dysfunction, which altogether result in BRB breakdown.[16] The summary of the pathophysiology is shown below (Figure 2).

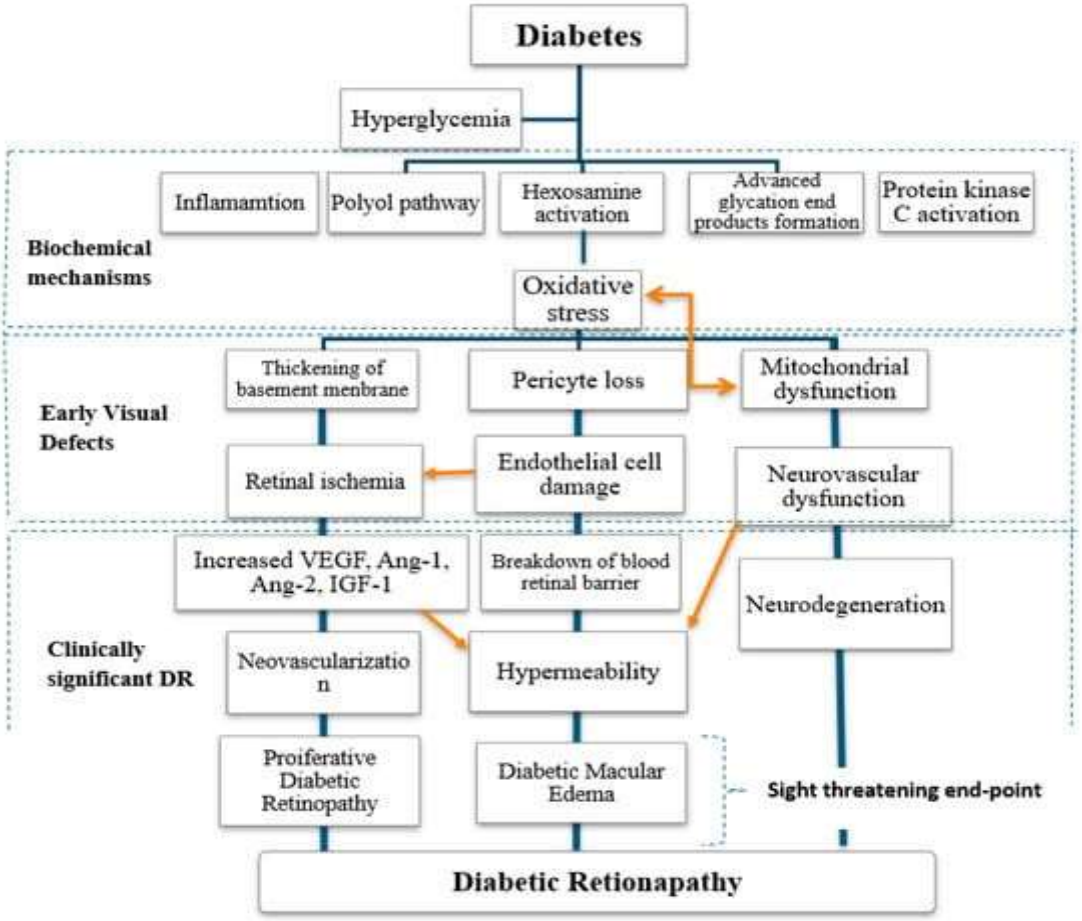

Figure 2: Diagrammatic synopsis of the Pathogenesis and Pathophysiology of DR.

Stages of diabetic retinopathy

National Institutional of Health (NIH)defines four stages of diabetic retinopathy:

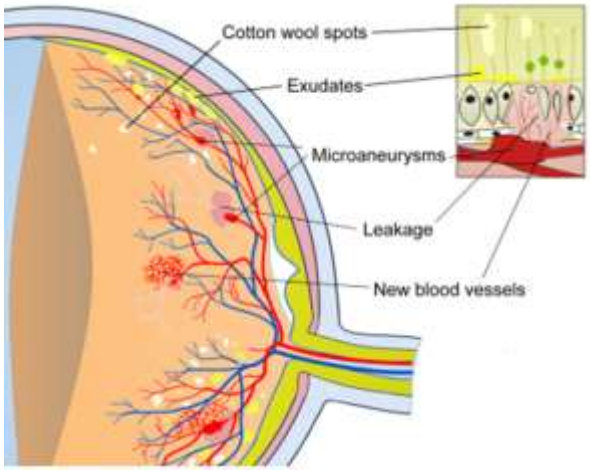

Fig. 3: Diagramatic representation of diabetic retinopathy stages.

Mild Nonproliferative form in which tiny capillaries experience swelling and leaking. These are called "microaneurysms."

a) Moderate nonproliferative form in which some of these capillaries are completely occluded depriving the retina of nourishment.
b) Severe nonproliferative form in which many capillaries are blocked and more of the retina does not receive needed nutrients. This triggers the body to grow new blood vessels to supply the deficit. These new blood vessels are weak, and tend to leak blood and fluids that can cause severe vision loss if not treated. In addition, "cotton wool" spots may appear on the retina, evidence of nerve fiber damage. These are a hallmark of pre- or non-proliferative diabetic retinopathy. These look like fluffy white spots that develop as a result of diabetic retinopathy or hypertension. In addition to cotton wool spots are hard exudates which are similar to the drusen seen in macular degeneration.
c) Proliferative form is an advanced stage of diabetic retinopathy. New, fragile capillaries grow both within and along the surface of the retina and into the vitreous of the eye. The additional growth may not cause vision loss by itself, although portions of the retina can be distorted, in turn distorting vision. Because the new capillaries are thin-walled and fragile, they are at great risk of leaking.
d) Ketosis may also develop if insulin production is insufficient. Ketosis occurs when the body starts burning fat instead of carbohydrates for energy. It arises from profound reduction in beta-cell mass (the cells that produce insulin) and results in ketone formation. Ketosis can become dangerous when ketones accumulate to too-high levels, leading to dehydration and changes to the chemical balance of your blood.

Treatment

a) Synthetic drugs in the treatment of diabetic retinopathy[18],[19]

1. Bevacizumab

Category- Antiangiogenic agents.

Uses-treatment of malignance and diabetic Retinopathy.

Mechanism of action

149 kDa recombinant humanized monoclonal antibody comprised oftwo mouse antibody binding regions targeting VEGF-A, with atruncated human IgG1 heavy chain.

2. Ranibizumab

Category- vascular endothelial growth factor A (VEGF-A) antagonists.

Uses- treat neovascular age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, myopic choroidal neovascularization, and diabetic retinopathy.

Mechanism of action

48 kDa recombinant monoclonal antibody fragment with one VEGF-A binding site, created from the same mouse antibody as bevacizumab,but lacking the fragment crystallizable (Fc) region and small enough toavoid Fc recycling and can more easily penetrate retinal tissue.

3. Aflibercept

Category- vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) antagonists.

Uses- treatment and management of neovascular age-related macular degeneration, diabetic macular edema, myopic choroidal neovascularization, macular edema associated with retinal vein occlusion, and diabetic retinopathy.

Mechanism of action

115 kDa recombinant soluble decoy receptor with two VEGF-bindingdomains, one each from VEGF-1 and VEGF-2 receptors, fused with Fcfrom IgG1. Traps VEGF-A, VEGF-B and PIGF and directs them to beconsumed by phagocytes.

4. Brolucizmab

Category-.vascular endothelial growth factor A (VEGF-A) antagonists

Uses- treat wet age-related macular degeneration and diabetic retinopathy.

Mechanism of action

26 kDa humanized monoclonal single-chain variable fragment. It bindsVEGF-A with a single binding site in a 2:1 brolucizumab: VEGF ratio.

5. Faricimab

Category- Bispecific Monoclonal Antibody

Uses- Treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD)

Mechanism of action

149 kDa dual-mechanism antibody with two different antigen-bindingfragment regions, one which targets VEGF and the other targetingAng-2, connected to a single Fc domain.

b) Natural products in the treatment of diabetic retinopathy

1. Turmeric (Curcuma longa)

The plant Tulsi or Holy Basil (Botanical name *Ocimum Sanctum*) belongs to family *Lamiaceae*. It is a tropical plant which grows as weed and also cultivated. Tulsi is worshipped by Hindus and is an important symbol of Hindu religion. It is a very common sight to find Tulsi Vrindavan (A special structure where tulsi is grown) in houses of Hindus. Texts of ayurveda describe the properties of tulsi as follows. It is light to digest and dries tissue secretions. Tulsi tastes hot and bitter. It can penetrate deep tissues and has anti helmenthic properties. Due to these properties it normalizes kapha and vata. Leaves, flowers, seeds and roots of Tulsi are used in

ayurvedic preparations. Apart from these researches have shown that tulsi is very effective in reducing blood sugar and blood cholesterol. It is anaturally available antioxidant. It is also a neuroprotective agent. Intraperitonel administration of 5ml/kg to 10ml/kg to rats reported a protective role in selenite induced experimental cataract. A combination of Vitamin E and Ocimum Sanctumtreatment also reported to reverse the change of Diabetic Retinopathy. The aqueous extract of the leaves of the Ocimum sanctum decrease the level of blood glucose in both alloxan and STZ induced diabetes in rats. Eugenol the active constituent of the plant is responsible for all the therapeutic action.Leaf extract increase the secretion of insulin by physiological pathway in animal model.

2. 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.[20] 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.

3. Ocimum sanctum(tulsi)

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).[21] 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 (PH 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 www.ejbps.com Jayasree et al. European Journal of Biomedical and Pharmaceutical Sciences 192 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, HbA1c, improved lipid profile and elevated the antioxidant enzymes. Fluorescein angiography of combined treated diabetic rats showed remarkable improvements.[22]

4. Fenugreek (Trigonellafoenum-graecum)

Fenugreek (*Trigonella foenum-graecum*) is an annual plant. It is belong to the family *Fabaceae*, Its leaves consisting of three small obovate to oblong leaflets. It is cultivated worldwide as a semiarid crop, and its seeds are used commonly as an ingredient in dishes from South Asia. Fenugreek is used as aherb (dried or fresh leaves), spice (seeds), and vegetable (fresh leaves, sprouts, and microgreens). Sotolon is the chemical responsible for fenugreek's distinctive sweet smell. Cuboid-shaped, yellow- to amber-coloured fenugreek seeds are frequently encountered in the cuisines of the Indian subcontinent, used as both whole and powdered form in Diabetic Retinopathy: Role of Traditional Medicinal Plants in its management and their molecular, the preparation of pickles, vegetable dishes, daals, and spice mixes such as panch phoron and sambar powder. They are often roasted to reduce bitterness and enhancement of flavour. In traditional medicine, fenugreek is thought to promote digestion, induce labour, and reduce blood sugar levels in diabetics, although the evidence for these effects is lacking. 42 It is reported in rats that protective effect in Diabetic Retinopathy was seen when *Trigonella foenum-graecum Linn*.(fenugreek) treatment provided to stz induced diabetic rats. Fenugreek treated retina have a marked decreased in the level of inflammation and angiogenic biomarkers. Retinal stress remain controlled. Lesser thickening of capillary of basement membrane reported in fenugreek treated rats.

5. Green tea (Camellia sinensis)

Green tea (leaves of *Camellia sinensis, Theaceae*) is a well known beverage among East Asia and it also posses traditional medicinal value. Green tea (GT) possesses anti-inflammatory, antioxidative and anticarcinogenic properties. The catechins present in GT are commonly known as polyphenols and are Diabetic Retinopathy: Role of Traditional Medicinal Plants in its management and their molecular. Flavanols in nature. Tea polyphenols such as epigallocatechin gallate (EGCG) havecryoprotective properties such as inhibition of proinflammatory cytokines and inhibition of growth factors by inducing neovascularization. Hyperglycaemia if prevented early can help in decreasing the microvascular complications associated with diabetes. Experimentally by Gupta and associates it is reported that green tea helps in controlling the thickness of basement membrane. TNF-α level is also comparable to the normal group rat. Expression of VEGF was not reported in rat treated with green tea.It is also reported in literature that the polyphenol Epigallocatechin gallate from green tea inhibit VEGF mediated angiogenesis. The study further reported that the treatment with green tea restore the antioxidant defence mechanism of Retina back to the normal. Green tea have potential to save the diabetic Retina.[23]

CONCLUSION

In conclusion, this review highlights the multifaceted nature of diabetic retinopathy treatment, emphasizing the potential of both synthetic and herbal approaches. While synthetic therapies, including anti-VEGF and corticosteroids, have proven effective in controlling the disease and preventing vision loss, they are often accompanied by adverse effects and economic burdens.

Conversely, herbal remedies present a promising complementary option, leveraging their antioxidant properties and anti-inflammatory effects to support ocular health. The traditional use of various plants, combined with emerging scientific evidence, underscores their potential role in a holistic treatment strategy.

Future research should focus on clinical trials to validate the efficacy and safety of herbal interventions, as well as explore synergistic effects when combined with conventional treatments. By integrating these approaches, we can pave the way for more effective, accessible, and patient-friendly management of diabetic retinopathy, ultimately improving patient outcomes and quality of life.

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