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Investigating Potential Pharmacotherapeutic Targets: Neuroinflammation and Neovascularization in Diabetic Eye Diseases (DEDs)

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Abstract

This review aims to raise awareness about diabetic eye diseases, including diabetic retinopathy (DR) and ocular angiosarcoma (ASO), which pose a significant risk of blindness among elderly widows. The challenging life of widows in this region, marked by economic and social isolation, contributes to various health issues, including heart disease, hypertension, diabetes, depression, and dementia. ASO, a rare malignant tumor, is characterized by neovascularization, neuroinflammation, and edema in ocular tissue. DR can progress to ASO when factors like diabetes, hypertension, and aging lead to increased oxidative stress. In the retina, microglia play a crucial role in causing inflammation, discomfort, and neurodegeneration, leading to vision loss. Key agents like AGE, VEGF, PKC, PARP, MMP9, NFkB, PDL-1, FVIII, and VWF are implicated in ocular neovascularization, neuroinflammation, and edema. The study focuses on identifying retinoprotective medications that can effectively treat DEDs by targeting the underlying mechanisms of neovascularization and neuroinflammation in the eye, providing potential therapeutic approaches for patients' benefit.

Keywords: Diabetic retinopathy, Ocular angiosarcoma, FVIII/VWF/VEGF, PDL-1/PD-1, Blood retinal barrier, Retinoprotective drugs.

Introduction:

Unraveling the Complexity of Diabetic Eye Diseases (DEDs) in North India: A Focus on Widow Populations [1]. This review sheds light on the etiopathogenesis of diabetic eye diseases, such as diabetic retinopathy (DR) and ocular angiosarcoma (ASO) [2], prevalent among elderly widows in North India [3], specifically in Vrindavan and Mathura, popular pilgrimage destinations. Referred to as the "city of widows," these areas house a substantial portion of India's 40 million-plus widow population, facing economic and social isolation [4],

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and an increased risk of health issues like heart disease, hypertension, diabetes, depression, and dementia. Among widows in ashrams [5], high blood pressure and diabetes are prevalent, further complicating diabetic eye diseases. DR, a disabling complication of diabetes mellitus, damages the retina's microvascular system [6], and early detection through automated techniques is essential. Factors like high blood pressure [7], high cholesterol, kidney disease, and genetic factors contribute to diabetic retinopathy [8]. ASO, characterized by neovascularization and neuroinflammation, is primarily[9] caused by retinal microvascular dysfunction and can manifest as microaneurysms and diabetic macular edema (DME). The review explores the involvement of various agents[10], including VEGF, MMP9, PARP, PKC, AGE, and NFkB, in the pathophysiology of DEDs [11]. Understanding these mechanisms can lead to potential therapeutic targets and retinoprotective medications to alleviate the impact of diabetic eye diseases on this vulnerable population [12].

Stages of Diabetic Retinopathy (DR):

Stage 1-DR: Characterized by the presence of small balloon-like bulges called microaneurysms in the ocular tissue [13]. These microaneurysms can lead to fluid leakage into the ocular tissue, and at least one microaneurysm is found in the retina [14].

Stage 2-DR: As the disease progresses, optic neuroinflammation may develop, causing distortion in the appearance of the eye [15]. Stages 1 and 2 may have distinct changes, but they are not mutually exclusive [16].

Stage 3-DR: Multiple blood capillaries become obstructed, leading to the deprivation of oxygen-rich blood in the choroid and retina [17]. This can stimulate angiogenesis and inflammation due to growth factors secreted by these tissues [18].

Late stage DR or ASO: In this advanced stage, retinal growth factors induce the sprouting of new blood vessels from the retina's inner surface into the vitreous gel surrounding the eye [19]. These delicate blood vessels are prone to rupture and bleeding. Scar tissue (sclerosis) forms, leading to irreversible retinal detachment and vision loss[20]. Thrombosis in ocular blood vessels can also cause scleral scar tissue formation [21].

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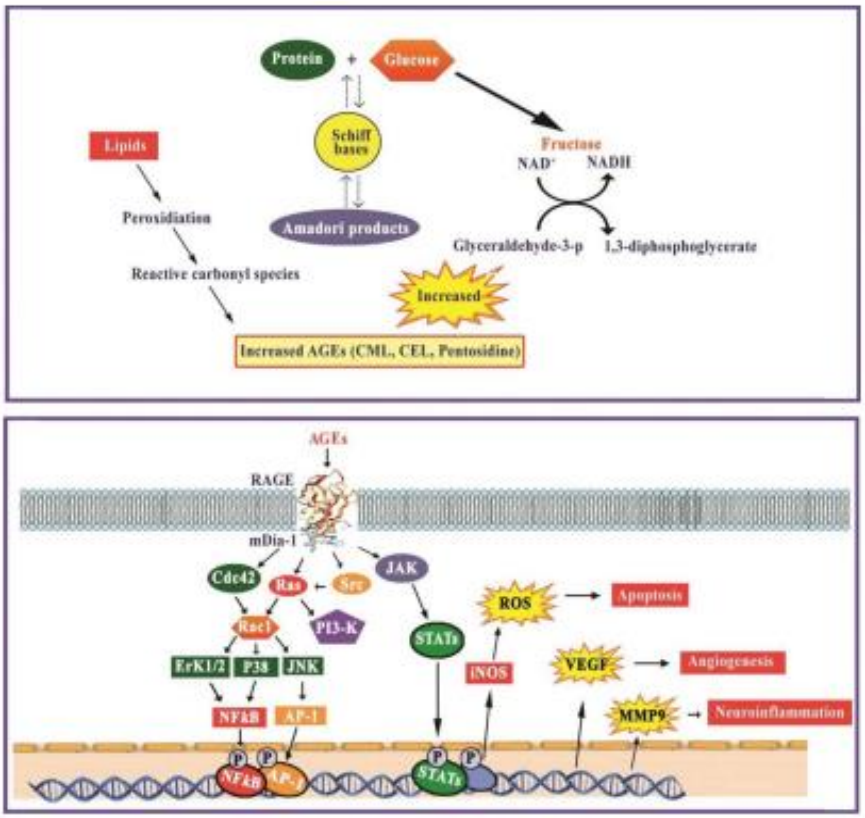

Fig. 1 Synthesis of AGEs and RAGE/AGE axis In human tissues, CML, CEL, and pentosidine are the three most common AGEs, respectively. Glyoxal (GO), methylglyoxal (MGO), and 3-deoxy glucosulose (3-DG) are reactive carbonyl species that combine to create AGEs. Oxidative stress on the retina promotes the AGE-RAGE axis, which was linked to ONV and eye neuroinflammation through activation of NF-kB. The NF-kB and AP-1 phosphorylation or activation are connected to the AGE-RAGE axis via RAS/MAPK/ERK1/2 signaling pathways. The JAK/STAT signal transduction pathway, which is connected to the AGE-RAGE axis, generated phosphorylated NF-kB (pNF-kB) and phosphorylated STAT3 (pSTAT3). The pNF-kB and pSTATs are responsible for the formation of MMP9 and VEGF. The ONV as well as neuroinflammation depend heavily on MMP9 and VEGF.

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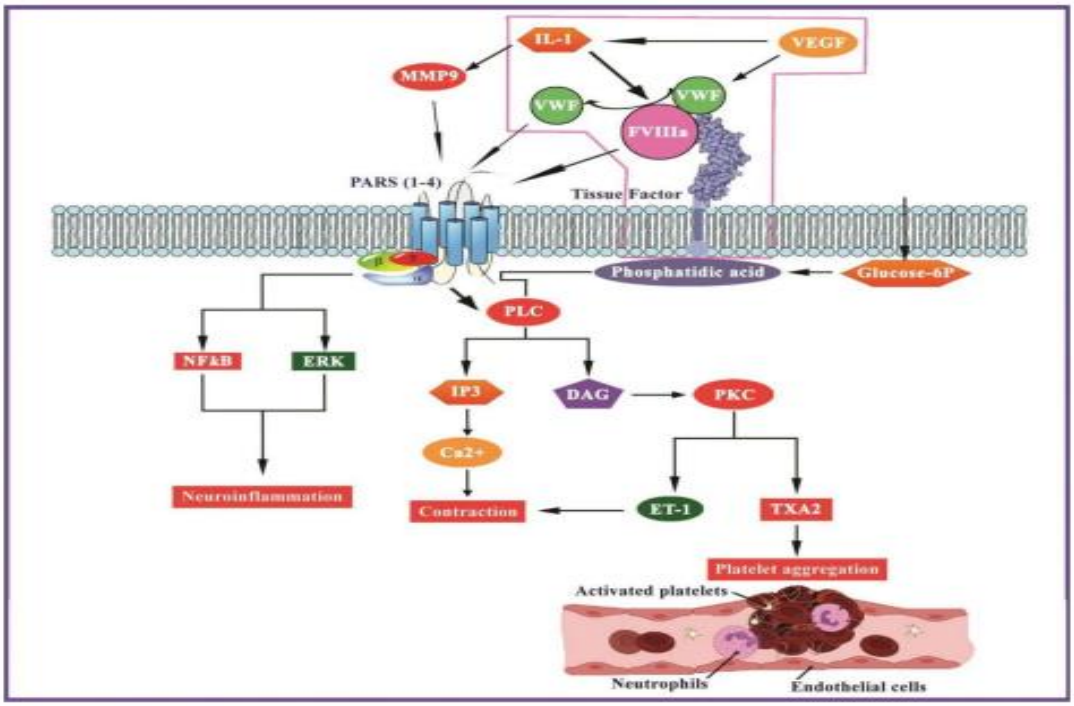
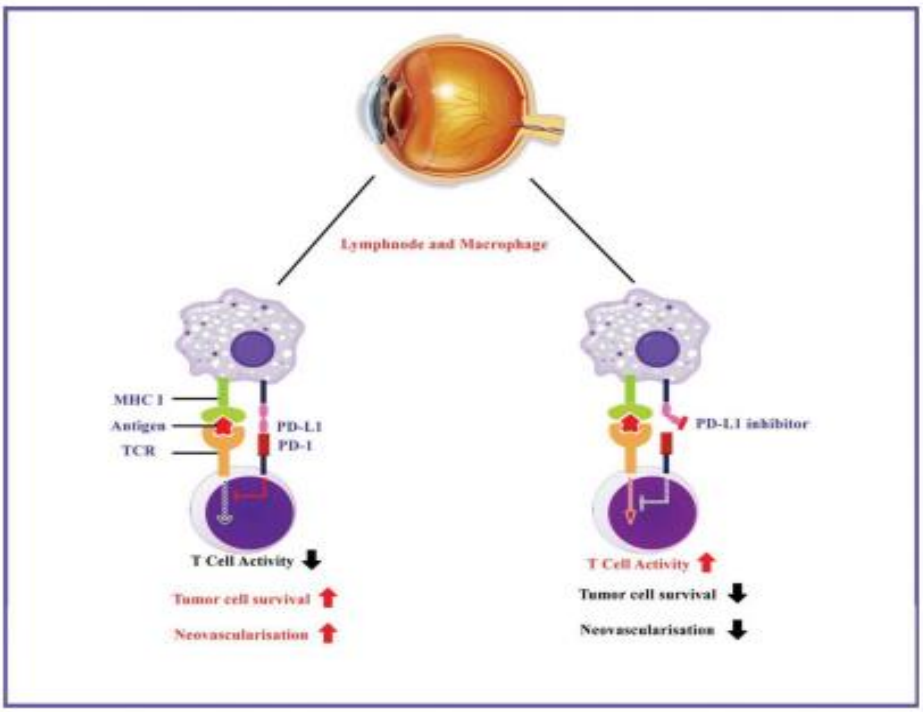


Fig. 2 The pathway of platelet aggregation and neuroinflammationThe FVIII was involved in a complex formation with the VWF (FVIII-VWF). When interleukin1 (IL-1) was overexpressed, activated VEGF took part in the proteolytic cleavage of FVIII-VWF, resulting in the generation of plasma-bound free activated FVIII (FVIIIa). DAG and calcium ions are the primary activators of the vast majority of PKC. Phosphatidic acid is converted to DAG via a series of intermediary metabolites generated by the cytoplasmic breakdown of glucose 6P. A variety of proteins, including VEGF, MMP9, NF-kB and inflammatory mediators, are produced more quickly when PKC isoforms are used in conjunction with their respective transduction systems to do so. An abundance of these protein components in retinal tissue is likewise linked to both the ONV and neuroinflammation. Thromboxane A2 (TXA2) and prostacyclin (PGI2) are disrupted when PKC is activated, resulting in blood vessel constriction and thrombosis. Activation of PKC increases production of the vasoconstrictor endothelin 1 (ET-1). Platelet aggregation is fueled by a TXA2/PGI2 imbalance and ET-1.

Fig. 3 PD-L1/PD-1 axis in ASO Tumor cells in the human body are detected and killed by T cells, but when tumour cells recognised PD1 protein on T cells, the tumour cells upregulated the PD-L1 proteins and PD-1 bound to PDL1, causing apoptosis of the T cells. T cell activation results in the production of interferon gamma (IFN-γ), which can increase the expression of PDL1 on tumour cell surfaces. The PD1/PDL1 signal transduction pathway plays a crucial role in tumour immunosuppression by dampening T-lymphocyte activation and bolstering tumor-cell immune tolerance



Retinoprotective Drugs:

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Phytoconstituents derived from neuroprotective herbal medicines have shown the ability to penetrate the blood-brain barrier and provide beneficial effects [22]. Moreover, several herbal remedies have been discovered that can cross the blood-retinal barrier (BRB) and protect the eye and optic nerve from neurodegeneration[23]. These remedies have been identified through extensive searches in multiple databases, including those used to treat neuropathy and protect the renal system from oxidative stress [24]. Additionally, various synthetic, peptide, and herbal medications with clinically proven retinoprotective properties and the ability to cross the BRB have been examined [25]. In the context of ocular angiosarcoma (ASO) therapy, the primary objective is to manage ocular neovascularization (ONV) and neuroinflammation [26]. Targeting the vascular endothelial growth factor (VEGF), which plays a crucial role in the development of new blood vessels, is essential for ONV therapy [27]. Inhibiting VEGF activity is a key treatment approach for neovascular eye diseases from table 1 [28].

Table 1 List of newer synthetic drugs that cross BRB and target VEGF

Type of newer anti-VEGF drugs	Preclinical/Clinical trial data/Model	Reference
CW-703 (12aa peptide)	Suppression of neovascularisation in a human umbilical vein macrovascular endothelial cells (HUVEC).	[89]
Adiponectin (cytokine)	Suppression of neovascularisation in VEGF- induced human umbilical vein macrovascular endothelial cells (HUVEC), human retinal microvascular endothelial cells (hREC) and human choroidal endothelial cells (hCEC).	[90]
RC-28-E, VEGF/bFGF dual decoy receptor (IgG1 Fc-fusion protein)	Suppression of laser induced Choroidal neovascularisation (CNV) in a monkey model	[91]
VEGFR1 + VEGFR2 + PDGFRβ (Ligand binding Fusion protein)	Suppression of laser-induced ONV in a mouse model	[92]
AXT 107 (peptide) (Derivative from collagen IV)	Suppression of Ischemia induced ONV and VEGF induced ONV in a mice model and rabbit eyes (2months) model.	[93]
PEDF 335 8-mer, PEDF 336 9-mer (peptides)	Suppression of laser-induced CNV (mouse model) after intravitreal injections	[94]
non-viral Sleeping Beauty (SB100X); peptide	Suppression of laser-induced ONV (choroid) in a rat model by ex vivo non-viral gene therapy	[95]
Human retinal progenitor cells (hRPCs)	Protection of retina using retinal degeneration rat model (intravitreal transplanted)	[96]
PEGylated APT-F2 (Aptamer)	Suppression of bFGF-induced ONV in a mouse model, laser-induced ONV in a mouse model, and ONV with fibrosis.	[97]
AS1411(Aptamer)	Suppression of murine corneal ONV after local application	[98]

Results and discussions:

The discussion highlights that diabetic eye diseases (DEDs) can lead to permanent vision loss due to increased ocular neovascularization (ONV), vascular tissue growth, and leukocyte infiltration in the retinal vasculature [29]. The involvement of various intermediate proteins and growth factors in the pathogenesis of DEDs has been outlined [30]. Effective management of DEDs is possible with appropriate medications or treatment approaches, as evaluated in this

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study. Vascular endothelial growth factor (VEGF) plays a dual role in DED formation, contributing to both ONV and the cleavage of the FVIII-VWF complex, leading to platelet aggregation and thrombosis[31]. The activation of protein kinase C (PKC) through DAG and calcium ions also promotes ONV by disrupting the thromboxane A2/prostacyclin (PGI2) axis and increasing the production of vasoconstrictor endothelin 1 (ET-1). However, despite extensive laboratory testing [32], many drugs are still unproven in terms of efficacy and safety [33]. The study indicates that anti-VEGF drugs have shown promise in the therapy and suppression of DEDs [34].

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