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The effects of SOD Melon Gliadin as an Antioxidant on VEGF and TGF β blood serum and vitreoretina in hyperglycemia rat model a literature review

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Abstract: Diabetes Mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, action, or both. Persistent hyperglycemia can lead to organ damage, including ocular complications such as diabetic retinopathy. Diabetic retinopathy is a primary cause of preventable blindness and can become vision-threatening if complications are persistent. Over one-third of individuals with diabetes exhibit signs of diabetic retinopathy, and among them, approximately one-third experience vision-threatening diabetic retinopathy (VTDR), defined as severe non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), or the presence of diabetic macular edema (DME). Diabetic retinopathy triggers the production of reactive oxygen species (ROS). Excessive accumulation of ROS can damage tissues surrounding retinal blood vessels, leading to oxidative stress that compromises the blood-retina barrier (BRB). Vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β) are two markers that indicate retinal dysfunction. Cells possess an intrinsic defense system against ROS, comprising antioxidants such as superoxide dismutase (SOD), glutathione reductase, glutathione peroxidase, and catalase. SOD melon gliadin (Glisodin®) is a potent antioxidant that elevates endogenous SOD levels, reduces ROS, and protects retinal tissues from damage and cell death. Research on SOD melon gliadin (Glisodin®) shows its potential as an antioxidant for preventing diabetic complications in the retina, specifically diabetic retinopathy.

Keywords: *Blood Serum, Diabetes mellitus, Glisodin, TGF β, VEGF, Vitreoretina.*

1. Introduction

Diabetes Mellitus is a chronic metabolic disease characterized by hyperglycemia due to impaired insulin secretion, action, or both. Diabetes-related complications can affect both macrovascular and microvascular systems. Diabetic retinopathy is a microvascular complication of diabetes mellitus, contributing significantly to morbidity associated with the disease. The global prevalence of diabetes in adults has been rising over recent decades. According to the International Diabetes Federation (IDF), 1 in 11 adults aged 20 to 79 years had diabetes mellitus globally in 2015. By 2021, this number will increase to an estimated 537 million people, with projections reaching 643 million by 2030 and 783 million by 2045. [1]. Diabetic Retinopathy (DR) is the leading cause of vision loss in adults aged 20 to 74 years. From 1990 to 2010, DR ranked as the fifth most common cause of preventable blindness and the fifth most common cause of moderate to severe visual impairment. In 2010, among an estimated 285 million people with diabetes worldwide, over one-third displayed signs of DR, and one-third of these cases were vision-threatening diabetic retinopathy (VTDR), which includes severe non-proliferative DR, proliferative DR (PDR), or diabetic macular edema (DME). The prevalence of DR varies across regions, with rates in most Asian countries reported between 12.1% and 23.0%, and VTDR prevalence between 4.3% and 4.6%. In Indonesia, the prevalence of diabetes mellitus is approximately 6.9%. Research

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conducted in Bali from 2005 to 2010 reported a DM prevalence of 5.9%, with 43% of these patients experiencing DR complications and 26.3% developing PDR.[2,3]

Diabetic retinopathy arises from a multitude of contributing factors, with chronic inflammation being a primary factor influencing the onset of diabetes mellitus and its associated complications. Diabetic retinopathy is linked to increased production of reactive oxygen species (ROS). Excessive accumulation of ROS can inflict tissue damage within and around retinal blood vessels, as oxidative stress disrupts the integrity of the blood-retina barrier (BRB). In diabetes mellitus (DM), oxidative stress is heightened by elevated levels of free radicals. Within the vitreoretinal tissue, superoxide dismutase (SOD) serves as a crucial antioxidant, providing essential protection against the damaging effects of superoxide radicals. SOD effectively shields retinal tissues from oxidative damage to membrane phospholipids caused by free radicals. [4] A study by Saric et al. examined oxidative stress markers in the vitreous and blood serum of patients with diabetic retinopathy, revealing significant findings. In the vitreous of patients with proliferative diabetic retinopathy (PDR), levels of vascular endothelial growth factor (VEGF), lipid hydroperoxidation (LPO), and malondialdehyde (MDA) were significantly elevated ($p<0.05$) compared to non-diabetic individuals, while total SOD levels were slightly reduced ($p<0.05$). In the blood serum of PDR patients, markers of advanced oxidation protein products (AOPP), MDA, and SOD were significantly elevated ($p<0.05$), with a modest increase in VEGF ($p<0.05$) when compared to non-diabetic individuals. [5]

SOD melon gliadin (Glisodin®) is a form of exogenous superoxide dismutase (SOD) derived from melon (Cucumis melo sp.). Administering SOD from plant extracts containing antioxidants can be challenging due to the denaturation of antioxidants, especially when taken orally. This limitation can be overcome by coating SOD with lipid and protein layers. The wheat gliadin in Glisodin® is particularly effective for preserving the oral bioavailability of SOD. This approach—often referred to as protected SOD, encapsulated SOD, coated SOD, or bioactive SOD—describes formulations of SOD-gliadin designed to resist gastrointestinal degradation.[6,7] SOD melon gliadin (Glisodin®) has shown potential as an antioxidant that reduces ROS levels inhibits cell death, and mitigates angiogenesis, lipid peroxidation, and inflammation. While research on the effects of Glisodin® on diabetic retinopathy complications remains limited in ophthalmology, studies involving other sources of exogenous SOD have been conducted. Administration of SOD melon gliadin supplements in hyperglycemic rat models has shown promising antioxidant effects, suggesting it may protect against hyperglycemia-induced retinal complications, including diabetic retinopathy, by modulating VEGF and TGF-β levels in blood serum and vitreous retina. This research points to the potential future application of Glisodin® as a therapeutic antioxidant for ocular protection in diabetic patients.

1.1. The Impact of Diabetes Mellitus on the Progression of Diabetic Retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes mellitus and a leading cause of vision loss in middle-aged and elderly individuals. Approximately one-third of people with diabetes are affected by DR. The severe stages of DR include proliferative diabetic retinopathy (PDR), characterized by the abnormal proliferation of new retinal blood vessels, and diabetic macular edema (DME), where fluid accumulation and swelling occur in the central retina. DR is strongly associated with prolonged diabetes duration, hyperglycemia, and hypertension. Complex interrelated pathophysiological mechanisms triggered by hyperglycemia underline the development of DR. These mechanisms include genetic and epigenetic factors, increased production of free radicals, advanced glycosylation end products, inflammatory factors, and vascular endothelial growth factor (VEGF). [8] The pathogenesis of DR involves complex, interrelated mechanisms triggered by hyperglycemia, including genetic and epigenetic factors, increased free radical production, advanced glycation end-products (AGEs), inflammatory mediators, and elevated vascular endothelial growth factor (VEGF) levels. Hyperglycemia is regarded as the primary precipitating factor in diabetic complications, with chronic hyperglycemia inducing microvascular damage through four biochemical pathways: activation of protein kinase C (PKC), the hexosamine pathway, the polyol pathway, and the accumulation of AGEs. Extensive research has shed light on the molecular pathways involved in DR. Metabolic alterations triggered by hyperglycemia, such as activation of the polyol and hexosamine pathways, de novo synthesis of

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diacylglycerol via PKC, and the production of free radicals and AGEs, are central to DR progression. Emerging evidence further indicates that neurodegeneration, neuroinflammation, and renin-angiotensin system (RAS) activation also play significant roles in DR pathogenesis. Additionally, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum (ER) stress contribute to DR development, with mitochondrial impairment and oxidative stress being key areas of focus in recent reviews on DR pathology. {9,10]

The initial vascular changes in the retina observed in histopathology include basement membrane thickening, endothelial injury, subsequent disruption of tight junctions, and pericyte loss. The loss of pericytes leads to vascular dysregulation and unchecked endothelial cell growth due to the absence of transforming growth factor-β (TGF-β) normally produced by pericytes. These changes contribute to the development of microaneurysms and intraretinal dot hemorrhages, two of the earliest detectable clinical abnormalities in early non-proliferative diabetic retinopathy (NPDR). Basement membrane thickening and tight junction disruption are significant contributors to retinal capillary leakage. Although thickened, the basement membrane becomes dysfunctional, allowing the passage of intravascular contents—such as proteins, lipids, inflammatory mediators, and other plasma components—into the interstitial space. Vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines, including IL-1β, tumor necrosis factor (TNF), IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), are produced by retinal glial cells (Müller cells and microglia), the retinal pigment epithelium (RPE), and macrophages. These factors play essential roles in early microvascular impairment and contribute to the breakdown of the blood-retinal barrier (BRB). Elevated inflammatory mediator levels induce a chronic inflammatory state in the diabetic retina, leading to leukocyte activation, adhesion to vascular endothelium (leukostasis), and further BRB disruption, resulting in increased vascular permeability. Diabetic macular edema (DME), a primary complication of DR, is driven largely by VEGF and pro-inflammatory cytokines. Local synthesis within the retina serves as the primary source of these inflammatory mediators. The BRB breakdown and subsequent vascular leakage in the macular area lead to DME, which can progress from mild to severe forms. In NPDR, vascular changes such as basement membrane thickening, endothelial injury with tight junction disruption, and pericyte loss contribute to clinical features, including dot hemorrhages, microaneurysms, and hard exudates. As DR progresses to the pre-proliferative stage, endothelial damage triggers vasoconstriction due to the release of vasoconstrictors (e.g., endothelin-1 and thromboxane A2), exacerbating hypoxia due to capillary occlusion. In advanced stages of DR, severe hypoxia promotes neovascularization. These newly formed blood vessels often extend into the vitreous, where they are prone to rupture, increasing the risk of severe visual impairment.[8].

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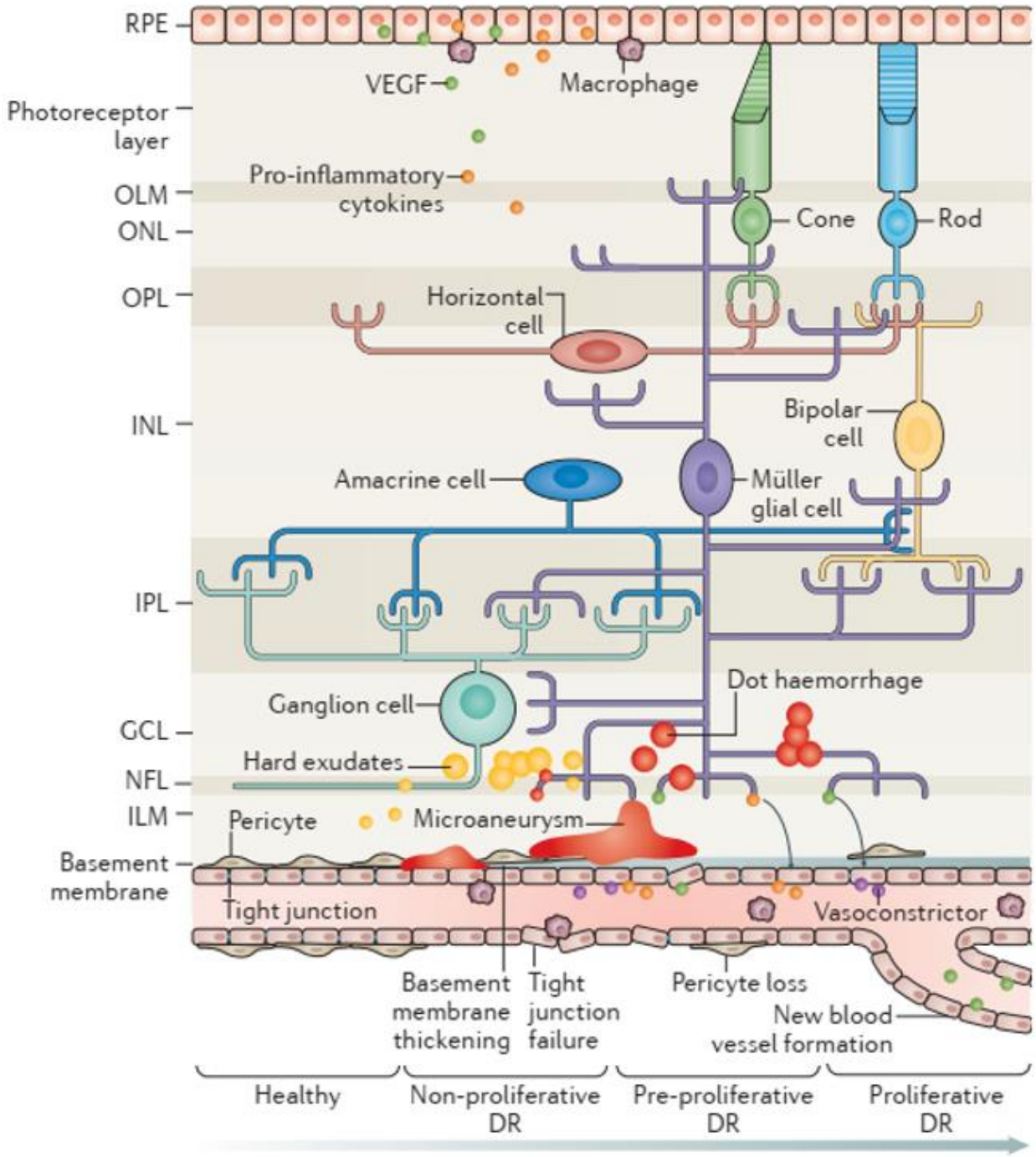

Figure 1.
Main pathogenic mechanisms in the development of diabetic retinopathy [8].

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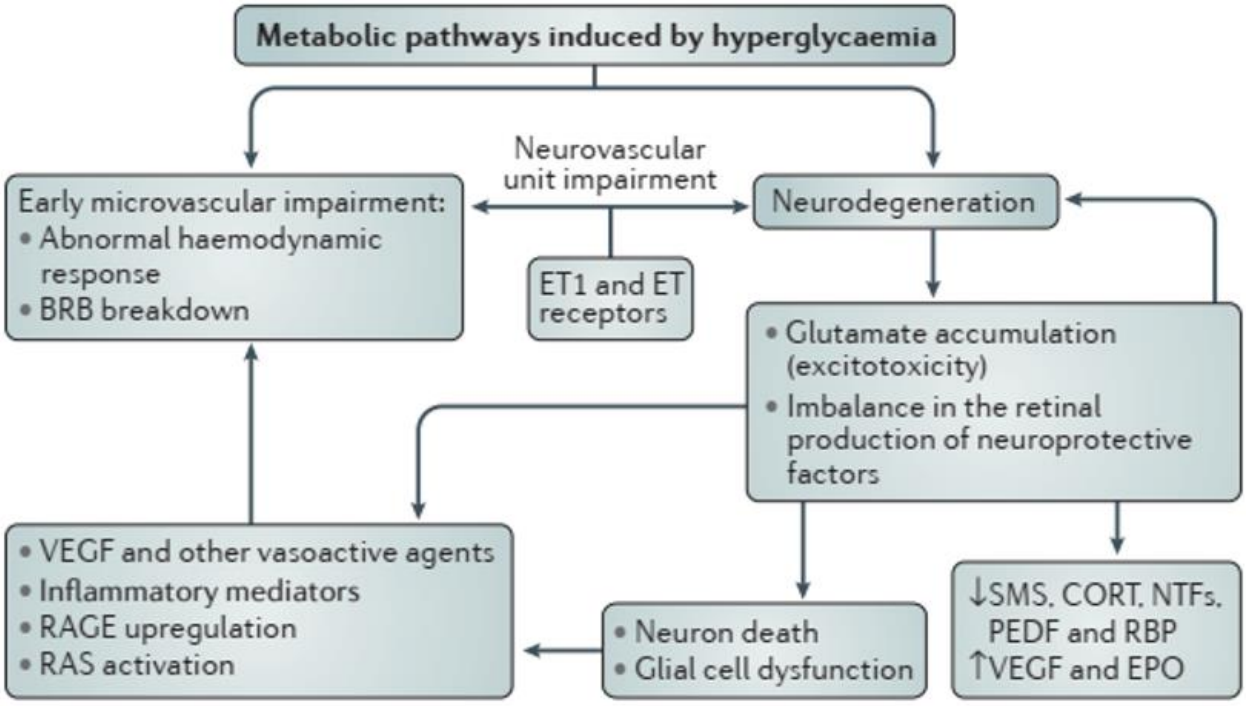

Figure 2.
Potential mechanisms linking neurodegeneration and microangiopathy in diabetic retinopathy [8].

The accumulation of glutamate in the extracellular space, specifically within the inter-synaptic cleft of retinal neurons—along with a reduction in the production of neuroprotective factors, are critical events leading to neuronal apoptosis and glial dysfunction. This process also triggers the overexpression of vascular endothelial growth factor (VEGF), which plays role in the disruption of the blood-retinal barrier (BRB).In addition to VEGF and other vasoactive agents, several factors link neurodegeneration with early microvascular impairment. These include the upregulation of inflammatory mediators, increased expression of receptors for advanced glycation end products (RAGE), and activation of the renin-angiotensin system (RAS). Furthermore, heightened intraretinal production of endothelin-1 (ET-1) has been shown to induce retinal neurodegeneration, thereby facilitating crosstalk between endothelial cells and the neuroretina. [8]

1.2. The Role of Diabetes Mellitus in Inducing Reactive Oxygen Species (ROS) and Their Impact on Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor Beta (TGF-β)

Chronic hyperglycemia leads to microvascular damage through four primary biochemical mechanisms: the polyol pathway, the protein kinase C (PKC) pathway, the accumulation of advanced glycation end-products (AGEs), and the activation of the hexosamine pathway. Hyperglycemia induced by these mechanisms can stimulate the production of reactive oxygen species (ROS), and excessive accumulation of ROS can cause significant damage to tissues surrounding retinal vessels. This oxidative stress negatively impacts the blood-retinal barrier (BRB). Vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β) serve as important biomarkers for retinal disorders. The accumulation of ROS and elevated VEGF levels within the eye play critical roles in the disruption of the BRB, while TGF-β is essential for maintaining ocular homeostasis. Research by Panahi et al. demonstrated a correlation between vitreous and serum VEGF levels in patients with proliferative diabetic retinopathy (PDR). They found that serum and vitreous VEGF levels were significantly lower in patients receiving oral diabetes therapy, those with well-controlled glycemia, and early-stage retinopathy patients. Additionally, Bonfiglio et al. investigated serum TGF-β levels in individuals with

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PDR, identifying serum TGF-β1 levels as predictive markers for disease progression from non-proliferative diabetic retinopathy (NPDR) to PDR. Cells possess a defense system against ROS, which includes antioxidants such as superoxide dismutase (SOD), glutathione reductase, glutathione peroxidase, and catalase. The SOD enzyme catalyzes the conversion of superoxide (O2−) to hydrogen peroxide (H2O2) and molecular oxygen (O2) and is present in all aerobic organisms, from bacteria to humans. The enzymatic activity of SOD was first discovered by biochemists Joe McCord and Irwin Fridovich, and its role as a major antioxidant defense mechanism is well established. SOD is crucial for delineating the balance between oxidant and antioxidant processes in ischemia/reperfusion-related pathologies in both humans and animal models.[13-16]

Research conducted by Zhang et al. investigated the levels of vascular endothelial growth factor (VEGF) and the kinase insert domain-containing receptor (KDR) in the vitreous humor of diabetic rats. Their findings revealed elevated levels of both VEGF and KDR in the vitreous of these diabetic rats. These alterations in VEGF and KDR levels are associated with the early onset of diabetes-induced retinopathy. Additionally, a study by Lee et al. demonstrated that intravitreal administration of superoxide dismutase 3 (SOD3) therapy improved Müller cell activation and mitigated pericyte dysfunction in diabetic mice. [17-18]

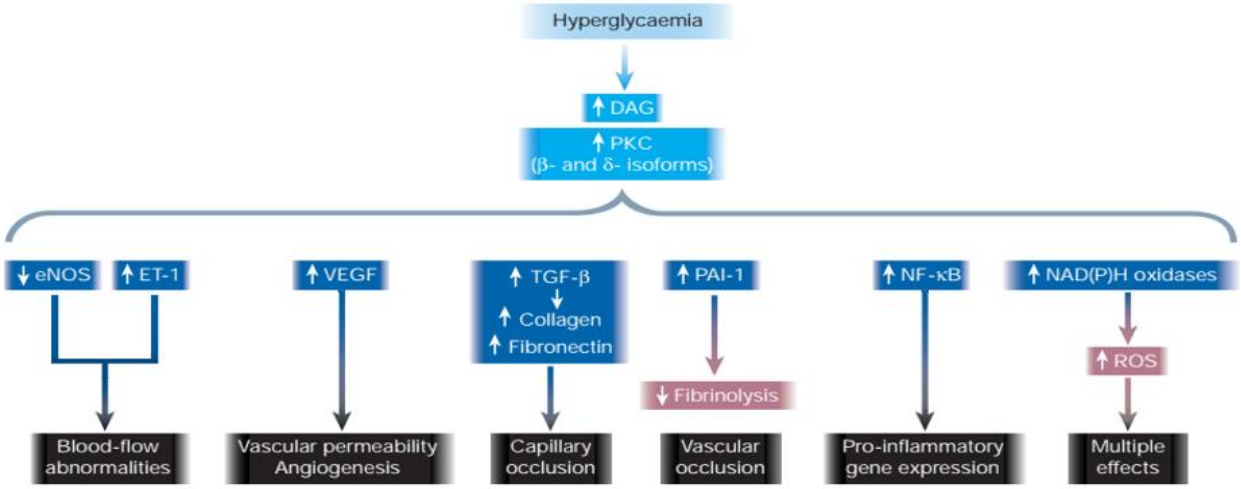

Figure 3.
Mechanisms of Hyperglycemia and Their Correlation with Increased VEGF and TGF β [10].

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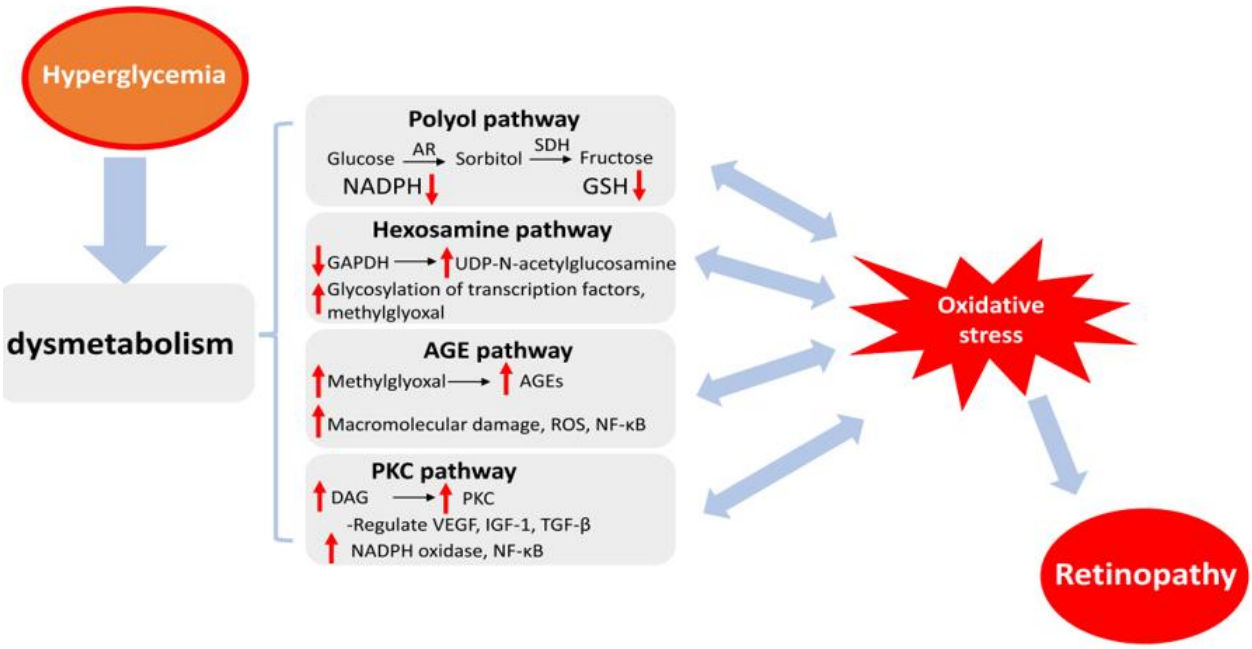

Figure 4.
Correlation VEGF, TGF β, SOD, ROS, and diabetic retinopathy [11].

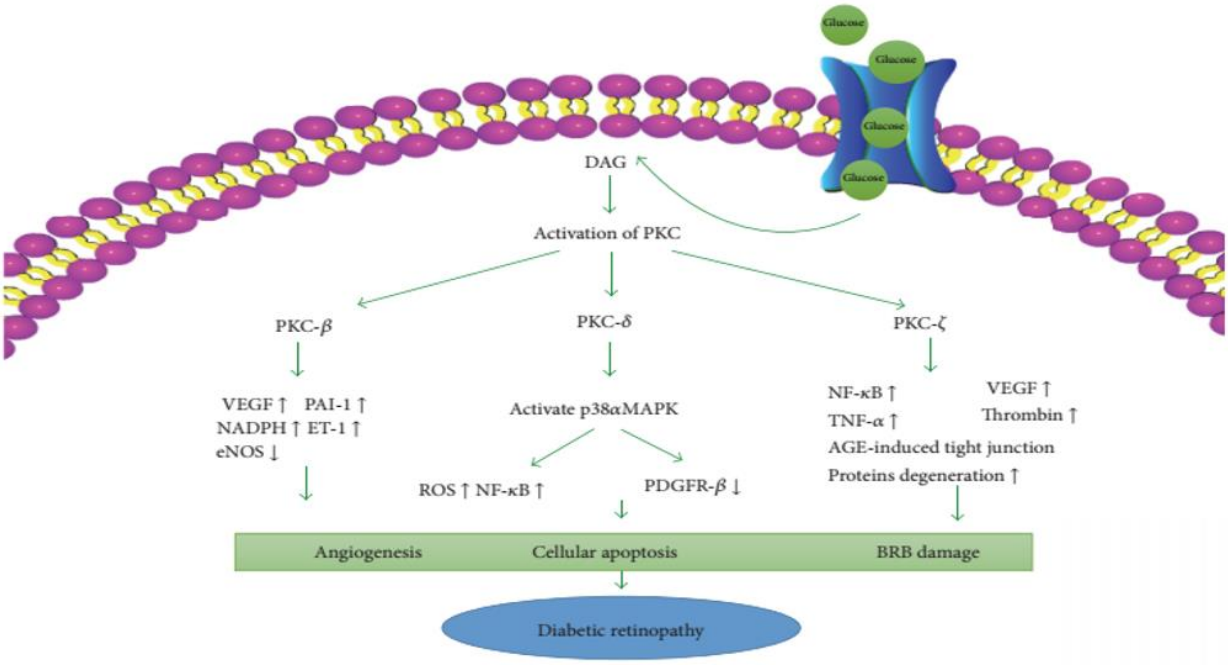

Figure 5.
Mechanism Diabetes, ROS, and blood-retinal barrier [12].

Transforming growth factor beta (TGF-β) is a proliferative growth factor that exerts its effects through multiple pathways, including the proliferation and migration of pro-fibrotic cells, both independently and via connective tissue growth factor (CTGF) in the eye. The TGF-β cytokine was first identified in the early 1980s, and three isoforms have been characterized in mammals: TGF-β1,

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TGF-β2, and TGF-β3. All three isoforms have been detected in the aqueous and vitreous humor of the human eye.Additionally, TGF-β is expressed in various ocular tissues, including the cornea, ciliary epithelium, crystalline lens, retina, and blood vessels. TGF-β1 and TGF-β2 demonstrate a distinct and specific distribution in the anterior segment of the human eye, whereas TGF-β3 has not been detected in any structures of the anterior eye[19]

Hyperglycemia and diabetes mellitus can activate the protein kinase C (PKC) pathway, leading to increased levels of vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β). These conditions also contribute to the induction of reactive oxygen species (ROS), promote angiogenesis, and facilitate cellular apoptosis, ultimately compromising the integrity of the blood-retinal barrier (BRB). The disruption of these processes significantly contributes to the development of diabetic retinopathy.

Table 1.
Expression and Role of TGF β in ocular pathology [19].

Gene	Human/Animal Model	Ocular Pathologies
TGF-β1↑	In human plasma	Primary open-angle glaucoma
TGF-β1↑	In human conjunctiva and minor salivary glands	Inflammatory ocular surface [138]
TGF-β2↑	In human aqueous humor	Proliferative vitreoretinopathy
TGF-β2↑	In human vitreous	Diabetic retinopathy
TGF-β2↑	In human aqueous humor	Open-angle glaucoma + increase of intraocular pressure in a glaucomatous eye
Activin A↑	In human vitreous specimens obtained from eyes with retinal ischemia	Regulation of angiogenesis and tissue fibrosis
BMP4↑	In adult retinal pigment epithelium-19 (ARPE-19) cells	Ocular angiogenesis associated with diabetic retinopathy via stimulation of VEGF by RPE cells
Loss of SMAD3	Human RPE-cell	Attenuation of PVR development
TGF-β1↑	In lens epithelium in mice	EMT-related fibrosis in lens epithelium

1.3. SOD Melon Gliadin (Glisodin®) as an Antioxidant in Opthalmology

The enzyme superoxide dismutase (SOD) facilitates the conversion of superoxide anions(O_2^-) into hydrogen peroxide (H_2O_2) and molecular oxygen (O_2). SOD is present in all aerobic organisms, from bacteria to humans. Its enzymatic activity was first identified by Joe McCord and Irwin Fridovich, who underscored its critical role in protecting organisms from the detrimental effects of reactive oxygen species (ROS). SOD functions as a metalloenzyme, requiring a specific conformation and the presence of copper and zinc, as well as one of the following cofactors: nickel, iron, or manganese. In humans, three isoforms of SOD are identified: extracellular copper-zinc SOD (SOD3), mitochondrial manganese SOD (SOD2), and cytosolic copper-zinc SOD (SOD1). It is important to note that SOD's catalytic action produces H_2O_2, which is classified as a reactive oxygen species and can be more accurately described as a pro-oxidant rather than solely as an antioxidant. Glisodin® is a rich source of SOD derived from melon (Cucumis melo) combined with wheat gliadin. Notably, SOD extracted from melon exhibits five to seven times greater activity than that from the classic "Charentais" melon. Gliadin, a biopolymer, serves to protect active molecules from enzymatic digestion. Research has demonstrated that the SOD activity of Glisodin® increases significantly and progressively in a medium that simulates the digestive process. Oral supplementation with melon-derived SOD combined with wheat gliadin has been shown to enhance endogenous antioxidant defenses. Recent studies indicate that gliadin may stimulate the release of zonulin from intestinal epithelial cells, which is involved in the modulation of intestinal

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permeability. This interaction with the intestinal epithelial barrier facilitates the release of active molecules into the mucous membrane, enabling SOD to enter the bloodstream. Rosa et al. reported that SOD3-deficient mice exhibit signs of premature aging beginning in the second month of life, characterized by a reduction in endothelial cell density in the cornea and increased susceptibility to acute inflammatory endothelial injury. In a comparative study utilizing an experimental rat model, researchers evaluated the pharmacological properties of SOD enzymes derived from rats, bovines, and humans. The results indicated that both human and bovine SOD enzymes demonstrated significantly greater pharmacological activity compared to their rat counterparts, despite exhibiting similar biochemical characteristics. In light of concerns regarding Creutzfeldt-Jakob disease, the availability of SOD products derived from cattle for human use has become restricted. Consequently, a viable alternative has been developed utilizing plant-derived SOD. Non-genetically modified melons from the species Cucumis melo L.C. are a particularly suitable source of this enzyme, exhibiting extremely high levels of SOD (100 U/mg) while containing comparatively lower amounts of other antioxidant components, such as 10 U/mg of catalase (CAT) and 1 U/mg of glutathione peroxidase (GPx). Ongoing research has led to the development of SOD-based compounds with potential therapeutic applications [7,20,21]

Research involving SOD Melon Gliadin (Glisodin®) in the field of ophthalmology was conducted by Sicard et al., who reported a significant reduction in reactive oxygen species (ROS) levels in the retinal layers of mice subjected to oxidative stress from light exposure. This reduction was achieved through the administration of oral melon-gliadin SOD over seven days. Additionally, a study by Yollamanda et al. investigated the use of Glisodin® as a therapeutic option for optic nerve trauma. The findings indicated no significant difference in the density of retinal ganglion cells between rats with optic nerve injury that received a combination therapy of methylprednisolone and SOD Melon Gliadin (Glisodin®) and those treated with methylprednisolone alone. As of now, there have been no studies specifically examining the effects of oral melon-gliadin SOD supplementation as a therapy for diabetic retinopathy. However, research by Lee et al. supports the utilization of recombinant extracellular SOD (SOD3) as a preventative treatment for diabetic retinopathy. Their study demonstrated that intravitreal SOD3 therapy improved the activation of retinal Müller cells and addressed pericyte dysfunction in diabetic mice. These results suggest that SOD3 provides a protective effect against the progression of diabetic retinopathy.[22-25]

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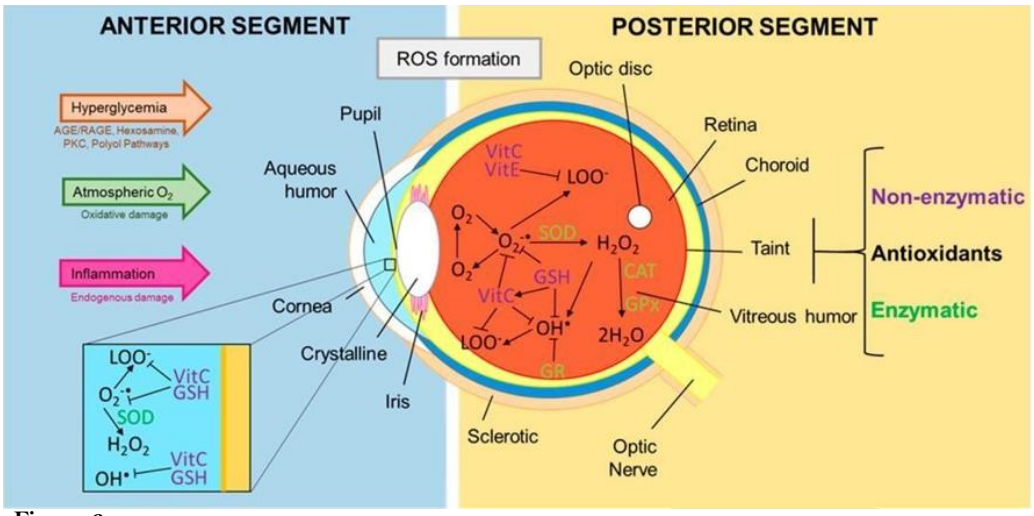

Figure 6.
ROS and antioxidant SOD in the anterior and posterior segments of the eye [24].

Table 2.
Animal research studies regarding the effects of administering SOD Gliadin[25].

Condition	Model	Supplementation	Effects	No effects	Other notes
IFN-γ/IgG1 IC activated Mφ	C57 BL/6 mice (ex vivo and in vivo)	SOD–gliadin 28 d 5 U-NBT/d	↓ $O_2^{\bullet -}$ production in cell cultures ↓TNF-α in cell cultures ↑IL-10 in cell cultures	n.s.	
Baseline healthy status	Balb/c mice (in vivo)	SOD–gliadin 28 d 0.1–5 mg/d	↑SOD activity in blood and liver ↑CAT, GPx activity in blood ↑RBCs resistance to hemolysis ↓Hepatocytes apoptosis	n.s.	Shows protection of SOD–gliadin in digestive track mimicking conditions
Type 2 diabetes	*db/db* mice (in vivo)	SOD–gliadin 12 wk	↓Albumin levels in urine ↓Oxidative stress in kidney	Body weight or glucose levels	
Type 2 diabetes	Wistar rats (ex vivo and in vivo)	SOD–gliadin 4 wk	↑SOD and CAT activity in heart ↑GSH levels in cardiac muscle ↓Cardimyocytes apoptosis ↓LPO in plasma	n.s.	Effects reported for SOD–gliadin-treated diabetic rats were compared with diabetic control animals
Ischemia/reperfusion injury	Aortic cross-clamping in pigs	SOD–gliadin 14 d 1250 U/d	↓DNA damage ↓Apoptotic cells in spinal cord	SOD, CAT, GPx levels in blood	No ameliorated organ function
Fibrosarcoma	C57 BL/6 mice (ex vivo and in vivo)	SOD–gliadin 30 d 10 mg/kg•d^{-1}	↑SOD activity in tumors ↓Metastasis development ↓Oxidative stress in tumors	SOD activity in blood Infiltrating cells in tumors Tumor incidence	Effects are lost after intraperitoneal administration of SOD–gliadin. Tendency for reduction on tumor growth with supplementation
Viral infection	FIV-infected cats	SOD–gliadin 30 d 100 mg/d	↑SOD activity in blood ↑CD4/CD8 ratio	GPx levels or oxidative stress in blood	
Cognitive memory	C57 BL/6 mice	SOD–gliadin 5 wk 100 mg/kg•d^{-1}	↓LPO in hippocampal neurons ↓Escape latency time ↑Neurogenesis	Body weight. Only slight increase on hippocampal SOD activity levels	Animal model of stress-induced impairment of spatial memory

2. Conclusion

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus and a leading cause of vision impairment and blindness when left untreated. One of the critical pathological processes in DR is the excessive accumulation of reactive oxygen species (ROS), which can damage tissues in and around

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the retinal vasculature. Increased ROS levels, particularly from the protein kinase C pathway, are associated with elevated vascular endothelial growth factor (VEGF) levels, which contribute significantly to blood-retinal barrier dysfunction and increased vascular permeability, leading to angiogenesis. Additionally, transforming growth factor beta (TGF-β) plays a vital role in maintaining ocular homeostasis and capillary integrity. SOD Melon Gliadin (Glisodin®) is a type of exogenous superoxide dismutase (SOD) derived from the melon (Cucumis melo sp.), recognized for its antioxidant properties. It is known to enhance endogenous SOD levels, reduce ROS, and mitigate damage to retinal vessels. Despite the potential benefits of Glisodin® in ophthalmology, particularly concerning complications associated with diabetic retinopathy, research in this area remains limited. However, studies involving other sources of exogenous SOD suggest that SOD Melon Gliadin could effectively elevate antioxidant levels in vitreoretinal tissue and serum, potentially aiding in the prevention of diabetic retinopathy in the future.

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