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Review Article

The Effects of Melon Superoxide Dismutase and Gliadin on Glutathione Reductase (GSH) and Superoxide Dismutase (SOD) Levels in Blood Plasma and Vitreoretina in Diabetic Rat Model: A Literature Review

Octarina Ervianti, Wimbo Sasono*, Reni Prastyani

ABSTRACT

Chronic hyperglycemia in diabetics causes microvascular damage through four mechanisms of biochemical changes, including activated protein kinase C (PKC) pathway, activated hexosamine pathway, increased polyol pathway, and increased advanced glycation end-products (AGEs), all of which will increase Reactive Oxygen Species (ROS) levels. ROS can damage proteins, nucleic acids, and lipids and hasten the onset of diabetes. ROS are produced in the presence of normal blood sugar levels, and the natural breakdown of glucose is controlled by insulin. Variables that regulate cellular respiration, including NAD-related substrates, oxygen, succinate, and antioxidant enzymes, modulate ROS levels and sustain cellular redox equilibrium. The conversion of superoxide anions into hydrogen peroxide, before subsequently metabolized into water by catalase and glutathione (GSH) peroxidase, is facilitated by the metalloprotein superoxide dismutase (SOD). Increased ROS levels can lead to diabetic complications, one of which is diabetic retinopathy. Melon superoxide dismutase (SOD) combined with gliadin (Glisodin®) is a potent antioxidant in counteracting free radicals that can reduce oxidative stress and prevent further cell death. Research related to the use of Glisodin® shows potential as an antioxidant agent with the hope of preventing diabetic complications.

Keywords: GSH, SOD, Blood Plasma, Vitreoretina, Diabetes Mellitus, Glisodin®

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INTRODUCTION

Globally, diabetes mellitus (DM) is a common chronic metabolic disease. Insufficient management of diabetes can result in a range of visual problems, including diabetic cataracts, diabetic retinopathy, and glaucoma. Diabetic retinopathy, the most common microvascular consequence of diabetes mellitus, is the main cause of vision impairment in adult Western populations. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) shows that diabetic retinopathy affects 60% of patients with type 2 diabetes and 99% of individuals with type 1 diabetes over the course of 20 years. By 2045, it is predicted that 387 million people (8.3% of the world's population) will have diabetes mellitus, with 6.9% of those cases occurring in Indonesia. Research in Bali from 2005 to 2010 revealed a 5.9% prevalence of DM. In the meantime, 43% of DM patients experience DR symptoms, and 26.3% of DM patients experience PDR complications.[1] Diabetic retinopathy arises from a multitude of factors,[2-4] with chronic inflammation being the main factor influencing the onset of diabetes mellitus and its associated complications. In diabetic individuals, white blood cells are essential for the deterioration of blood vessel walls, leading to atherosclerosis and the rupture of unstable plaques, which can result in thrombosis. Neutrophil-lymphocyte ratios (NLRs), which represent leukocyte subtypes, have been considered an accessible and reasonably priced inflammatory measure for basic blood tests.[5]

Mean platelet volume (MPV) is another hemogram parameter thought to be an unusual inflammatory marker. In critical care, there is evidence linking mean platelet volume to mortality. MPV may serve as a proxy for the inflammatory burden associated with type 2 diabetes and obesity. As MPV is inexpensive and simple to test, it may be screened regularly in these patients, along with HbA1c and other parameters, to keep doctors and patients informed about the inflammatory burden of these diseases.[6] According to Jauhar et al., patients with type 2 DM had higher NLR values than controls, which may indicate a long-term steady state of inflammation in these individuals. However, the level of glycemic control had no bearing on the NLR readings.[7]

In diabetes mellitus (DM), there is increased oxidative stress triggered by elevated levels of free radicals due to retinal tissue experiencing both increased production and decreased removal of these radicals. Within vitreoretinal tissue, superoxide dismutase (SOD) acts as the principal antioxidant, providing vital defense against the detrimental effects caused by superoxide radicals. SOD effectively protects retinal tissue from oxidative damage to membrane phospholipids caused by free radicals. Glutathione (GSH) is recognized as the primary protective mechanism in the retina, serving as a protective agent by counteracting the damaging effects of reactive oxygen species (ROS) and contributing to the maintenance of the cell's normal redox state.[8] Melon superoxide dismutase combined with gliadin is a type of exogenous SOD derived from

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melon (Cucumis melo sp.). Administering SOD using plant extracts containing antioxidants is often ineffective because the antioxidants become denatured, particularly when taken orally. This challenge can be addressed by applying a layer of lipids and proteins to the surface of SOD. The wheat gliadin found in Glisodin® serves as an effective method for preserving the oral bioavailability of SOD.[9] Gliadin protects SOD from degradation in the stomach due to its bioadhesive properties, which enhance its attachment to the small intestine's epithelium and extend its presence in the gastrointestinal tract. In addition to preventing ROS accumulation, Melon SOD combined with gliadin has the potential to reduce cell death by inhibiting fatty peroxidase and DNA damage in cells. It is also known to have an anti-inflammatory role by preventing neutrophil infiltration and reducing the production of proinflammatory cytokines. In the field of ophthalmology, research on the effect of Glisodin® on diabetic retinopathy complications is still very limited, but studies using preparations from other exogenous SOD sources have been conducted. The administration of exogenous SOD is known to increase antioxidant levels in vitreoretinal tissue and serum blood plasma, which is expected to help prevent diabetic retinopathy.[10]

Development and progression of diabetic retinopathy

Hyperglycemia is considered the main precipitant of diabetic complications. Chronic hyperglycemia causes microvascular damage through four mechanisms of biochemical changes: activation of the protein kinase C (PKC) pathway, activation of the hexosamine pathway, increase in the polyol pathway, and increase in advanced glycation end-products (AGEs).[3, 11]

In the polyol pathway, glucose is first metabolized into sorbitol and then into fructose. Under normal circumstances, the enzyme that initiates this process, aldose reductase, has a low affinity for glucose. High sorbitol levels lead to pericyte apoptosis, endothelial cell death, and basement membrane thickening. Aldose reductase plays a pivotal role in this pathway by inducing cell damage, as it reduces toxic aldehydes to inactive alcohols. With high glucose concentrations, aldose reductase enables the conversion of glucose to sorbitol. Sorbitol dehydrogenase then oxidizes sorbitol to fructose. NADPH, a cofactor required by this enzyme, is essential for replenishing intracellular antioxidants like glutathione. Disruption of the glutathione regeneration process reduces glutathione levels, thereby increasing cell vulnerability to oxidative stress.[2, 3, 12-14]

Protein kinase C (PKC), a serine-threonine kinase, is responsible for regulating proteins. PKC comprises 11 isoforms, with nine being activated by diacylglycerol (DAG). Three isoforms—PKC-β, PKC-δ, and PKC-ζ—are specifically implicated in diabetes. High blood glucose levels generate ROS and synthesize DAG, which eventually activate PKC. Hyperglycemia predominantly triggers PKC-β activation, leading to cell and tissue hypoxia by causing irregularities in blood vessels and capillaries. This is achieved by diminishing nitric oxide generation and/or enhancing endothelin-1 activity, along with a reduction in endothelial nitric oxide synthase (eNOS) levels in endothelial cells. Additionally, PKC is involved in the overexpression of TGF-β, the activation and regulation of many membrane-associated NAD(P)H-dependent oxidases, the activation of NF-kB, and the suppression of fibrinolysis through PAI-1 when triggered by hyperglycemia. NF-kB activation triggers the expression of proinflammatory mediators, while ROS expression triggers oxidative stress. Decreased production of eNOS and increased ET-1 result in abnormalities of blood flow. Meanwhile, increased expression of TGF-β and PAI-1 results in capillary and vascular occlusion. PKC activation also triggers the expression of VEGF, which is an important factor for vascular permeability and angiogenesis.[2, 3, 11, 15, 16]

Increased ROS levels caused by hyperglycemia impair the activity of glyceraldehyde-3-phosphate dehydrogenase. The hexosamine pathway replaces fructose-6-phosphate in the glycolysis process due to the action of this enzyme. Glycolysis is the primary method of consuming glucose, starting with glucose and proceeding to glucose-6-phosphate, fructose-6-phosphate, and finally ending with pyruvate. The enzyme GFAT (glutamine fructose-6-phosphate amidotransferase) transforms a portion of the generated fructose-6-phosphate into UDP-N-acetylglucosamine. Subsequent changes in UDP-N-acetylglucosamine modify serine and threonine residues on transcription factors. When glucosamine is excessively modified, it disrupts gene transcription, causing heightened modification of the transcription factor Sp1 and consequently boosting TGF-β1 and PAI-1 expression. Both of these expressions cause adverse effects on the vascular system of patients with DM.[2, 3, 11]

Nucleic acids, lipids, and proteins undergo non-enzymatic reactions with amino groups, leading to the formation of AGEs. These reactions occur due to increased blood glucose levels, a condition known as hyperglycemia. Under normal circumstances, AGEs begin to form from embryonic development and accumulate over time, but their formation increases under hyperglycemia. AGEs are amino acids or lipids that are glycated or oxidized without enzymatic processes following exposure to aldose sugars. There are three important mechanisms that occur due to AGE formation under hyperglycemia conditions. The initial mechanism involves modifying intracellular proteins, including those that regulate gene transcription. The extracellular matrix of nearby molecules is altered by the dispersion of AGE precursors from the cell, constituting the second mechanism. As a result of this alteration, the connection between the matrix and the cell is disrupted, leading to the third mechanism, which causes cellular dysfunction and programmed cell death. The efflux of AGE precursors from the cell subsequently modifies proteins dispersed inside the cell. These modified proteins then bind with the receptor for advanced glycation end-products (RAGE), triggering reactive oxygen species (ROS) activation. The production of proinflammatory cytokines and growth factors, including granulocyte-macrophage colony-stimulating factor, interleukin-1 (IL-1), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor, macrophage colony-stimulating factor, transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF), is triggered by ROS-induced activation of nuclear factor kappa B (NF-κB). The appearance of growth factors and proinflammatory cytokines results in increased vascular permeability and apoptosis of pericytes. Additionally, these cytokines induce the expression of ROS, resulting in a two-way mechanism for ROS production.[2, 3]

Diabetes-induced ROS formation

Oxidative stress has the capacity to harm the retina and other specific organs. There are two main factors that affect the production of reactive oxygen species (ROS): the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) system and mitochondrial oxidative phosphorylation. As the main internal source of ROS, mitochondria utilize 95% of the available oxygen for ATP production. In the electron transport chain, around 2% of oxygen is incorporated and further oxidized, leading to the production of superoxides like hydrogen peroxide and O2-. The disturbance of mitochondrial electron transport in diabetes results in excessive superoxide generation. Numerous abnormal biochemical metabolic pathways, such as the AGE, PKC, and polyol pathways, can be triggered by this overproduction. Several studies have shown that in the retinas of people with diabetes, transcription levels for cytochrome b of complex III, as well as mitochondrial DNA-encoded NADH dehydrogenase 1 and 6 of complex I, are below average. This anomaly contributes to the advancement of diabetic retinopathy. The combination of superoxide and nitric oxide produces peroxynitrite, which has the capacity to oxidize low molecular weight antioxidants, including tetrahydrobiopterin, cysteine, and glutathione

(GSH). The oxidation process causes cytotoxicity by inducing lipid peroxidation, oxidizing sulfhydryl groups, which deactivate enzymes, causing tyrosine nitration, and damaging DNA.[11]

The Nox system can generate ROS and help transform molecular oxygen into superoxide and/or hydrogen peroxide. This process involves the assimilation of electrons from NADPH and their subsequent transfer to molecular oxygen. Oxidative stress in the vascular system is largely attributed to the Nox system, which encompasses numerous isoforms. Nox 4, Nox 2, and Nox 1 isoforms are widely distributed in the vascular system. Elevated Nox 2 activity has been observed in the retina of diabetic rats. The escalation of this phenomenon is linked to increased ROS generation, upregulated expression of vascular endothelial growth factor (VEGF), and intercellular adhesion molecule-1 (ICAM-1). Nevertheless, this issue can be averted by eliminating the Nox 2 gene. Similar outcomes have also been observed in the renal blood vessels, the coronary microvasculature, and the endothelial cells of the aorta.[11]

Antioxidants

Antioxidants are natural or man-made substances that help counteract or delay cell damage caused by oxidation. Antioxidants are volatile compounds synthesized within the body and can also be obtained from food sources. Under normal bodily conditions, the human antioxidant defense system removes excessive ROS. The antioxidant system comprises enzymatic antioxidants such as catalase (CAT), α-tocopherol (Vitamin E), glutathione peroxidase (GPx), all-trans-retinol (Vitamin A), and superoxide dismutase (SOD), as well as non-enzymatic antioxidants, including β-carotene, glutathione (GSH), thioredoxin (TRX), ascorbic acid (Vitamin C), and glutathione transferase (GST). Antioxidants are crucial in the prevention of many diseases, including cancer, cataracts, cardiovascular disease, glaucoma, muscle degeneration, Alzheimer's disease, hypertension, autoimmune disorders, and neurological diseases. Antioxidants serve to inhibit the harmful effects of free radicals, mitigate the danger of infection, avert DNA damage, facilitate the optimal operation of crucial organs like the heart, and promote the maintenance of healthy skin.[17, 18]

ROS have the ability to harm nucleic acids, proteins, and lipids, contributing to diabetes development. ROS are produced during glucose metabolism under normal blood sugar levels, and insulin helps control this natural process. Variables that regulate cellular respiration, including NAD-related substrates, oxygen, succinate, and antioxidant enzymes, modulate ROS levels and sustain cellular redox equilibrium. The conversion of superoxide anions into hydrogen peroxide, before subsequently metabolized into water by catalase and glutathione (GSH) peroxidase, is facilitated by the metalloprotein superoxide dismutase (SOD). The conversion of oxidized glutathione (GSSG) back into its reduced form (GSH) is facilitated by glutathione reductase using NADPH. During typical conditions of reduction, the production of superoxide anions and hydrogen peroxide accounts for only approximately 1-2% of the overall oxygen consumption.[19]

Melon Superoxide Dismutase and Gliadin (Glisodin®)

The enzyme SOD facilitates the transformation of O2- into H2O2 and O2. SOD is found in all aerobic organisms, ranging from bacteria to humans. Its enzymatic activity was first identified by Joe McCord and Irwin Fridovich, who highlighted its essential function in shielding organisms from the harmful effects of ROS. There are various sources of exogenous SOD (Table 1). SOD is a metalloenzyme that relies on a specific conformation of the enzyme and necessitates the presence of copper and zinc, as well as one of the following cofactors: nickel, iron, or manganese. Three isoforms of SOD are found in humans: extracellular copper-zinc-SOD (SOD3), mitochondrial manganese-SOD (SOD2), and cytosolic copper-zinc-SOD (SOD1). It is more appropriate to refer to SOD's independent action as a pro-oxidant rather than an antioxidant because it produces H2O2 through its catalysis, which is classified as a reactive oxygen species (ROS). The presence of H2O2 is associated with the increased expression of important antioxidant enzymes like CAT and GPx. Therefore, by boosting oxidative stress signaling, an increase in SOD activity might activate other antioxidant enzymes. Depending on the origin of the enzyme, SOD supplementation can have different impacts. For instance, murine SOD has a lesser effect in mouse models compared to SOD derived from other species. Rosa et al. reported that SOD3 mice exhibit premature aging beginning in the second month, a decrease in endothelial cells in the cornea, and heightened vulnerability to acute inflammatory endothelium injury. Using an experimental rat model, researchers conducted a comparative study to evaluate the pharmacological properties of SOD enzymes sourced from rats, bovines, and humans. The results revealed that both human and bovine enzymes exhibited much greater pharmacological activity despite having similar biochemical features. Due to the emergence of Creutzfeldt-Jacob disease, the availability of SOD products derived from cattle for human use became restricted. As a result, a viable substitute was created using a form of SOD produced from plants. Nongenetically modified melons of the Cucumis melo L.C. species are a suitable source for this enzyme due to their very high levels of SOD (100 U/mg) and comparatively lower amounts of other antioxidant components such as 10 U/mg CAT and 1 U/mg GPx. Research developments have led to the development of SOD-based compounds for potential therapeutic applications (Table 2).[20]

Multiple research teams have developed various coverings for SOD encapsulation utilizing lipids and proteins to mitigate bioavailability concerns. Gliadin produced from wheat is the most extensively researched SOD coating. The study demonstrated that wheat gliadin has the ability to safeguard SOD from breaking down in the stomach while also exhibiting bio-adhesive qualities. This alteration in bio-adhesion has the potential to strengthen the binding of the enzyme to the epithelial cells of the small intestine. The large molecular weight of SOD makes it unlikely to be absorbed in the small intestine. While gliadin stimulates proteins that regulate junctions and perhaps enhance the permeability of the intestines, there is no evidence to suggest that SOD can pass through the intestinal barrier. Encapsulated SOD, bioactive SOD, protected SOD, and coated SOD are synonymous terms describing formulations of melon superoxide dismutase and gliadin that resist deactivation in the gastrointestinal system.[21]

Benefits of Melon Superoxide Dismutase and Gliadin (Glisodin®) in ophthalmology

Several studies have demonstrated the benefits of using Glisodin® against various systemic diseases. Research on the use of Superoxide Dismutase Melon and Glisodin® in ophthalmology has been conducted by Sicard et al., who discovered a substantial reduction in ROS levels in the retinal layer of mice subjected to oxidative stress induced by light exposure. This was achieved through oral administration of melon superoxide dismutase and gliadin for seven days.[22] Another study by Yollamanda et al. investigated the use of Glisodin® as a therapy for optic trauma. The study found no significant difference in retinal ganglion cell density in rat models of optic nerve trauma when comparing the combination therapy of methylprednisolone with melon superoxide dismutase and gliadin to the administration of either methylprednisolone therapy or melon superoxide dismutase and gliadin alone.[23]

To date, there have been no studies examining the effects of oral melon superoxide dismutase and gliadin supplementation as a therapy for diabetic retinopathy. However, research by Lee et al. supports the use of recombinant extracellular SOD (SOD3) as a preventive therapy for diabetic retinopathy. The study showed that intravitreal SOD3 therapy improved retinal Müller cell activation and pericyte dysfunction in diabetic rats, suggesting that SOD3 provides protection against the progression of diabetic retinopathy .[24]

Terrestrial Plants	Microbial	Cyanobacteria	Chromista	Marine Plants
Allium cepa L.	*Anabaena Geobacillus* sp.	*Anabaena cylindrica*	*Lingulodinium polyedrum*	*Avicennia marina*
Anacardium occidentale L.	*Bacillus amyloliquefaciens*	*Anabaena variabilis Kutz*	*Minutocellus polymorphus*	*Bruguiera gymnorrhiza*
Camellia sinensis	*Bacillus subtilis*	*Cyanobacterium synechococcus*	*Nitzschia closterium*	*Enteromorpha linza*
Cucumis melo L.C.	*Brucella abortus*	*Microcystis aeruginosa*	*Thallassiosira weissflogii*	*Platymonas subcordiformis*
Cucurbitamoschata L.	*Caulobacter crescentus*	*Nostoc commune*		*Porphyridium cruentum*
Fagopyrum tataricum	*Escherichia coli*	*Nostoc PCC 7120*		*Sonneratia alba*
Gossypium herbaceum L.	*Haemophilus influenzae*	*Plectonema boryanum*		*Tetraselmis gracilis*
Hordeum vulgare	*Haemophilus parainfluenzae*	*Plectonema boryanum*		
Luffa cylindrical	*Lactobacillus fermentum*			
Momordica charantia	*Nodularia Aphanizomenon*			
Momordicacharantia L.	*Photobacterium leiognathi*			
Nicotiana tabacum	*Photobacterium phosphoreum*			
Olea europaea L.	*Photobacterium sepia*			
Pisum sativum	*Pseudomonas aeruginosa*			
Rosmarinus officinalis *				
Saccharum spp.				
Salvia officinalis *				
Syzygium cumini				
Thymus officinalis *				
Vitis vinifera L.				
Zea mays L.				

* Culinary herbs with SOD mimetic activity.

Table 1: Main natural sources of exogenous SOD[20]

SOD/SOD Donor	SOD Mimetics	Gene Therapy
CAR-modified liposomes fasudil plus SOD	$[Fe(HPClNOL)Cl_2]NO_3$	SOD3-overexpressing MSCs
gliadin SOD	$MnTDE\text{-}2\text{-}ImP^{5+}$	
hEC-SOD	Calmangafodipir *	
MS-AOE®	EUK-134	
nano-SOD	EUK-207	
O-HTCC-SOD	GC4419 *	
PC-SOD	$Nano\text{-}MnTnBuOE\text{-}2\text{-}PyP^{5+}$	
rMnSOD *	Mangafodipir *	
SOD-loaded thermo-sensitive hydrogel-poly(*N*-isopropyl-acrylamide)/poly(γ-glutamic acid)	mito-tempo	
SOD-loaded porous polymersome	Mn1	
SOD *	$MnTE\text{-}2\text{-}PyP^{5+}$ *	
SOD1	$MnTM\text{-}4\text{-}PyP^{5+}$	
SOD2	$MnTnBuOE\text{-}2\text{-}PyP^{5+}$ *	
SOD2 by *Bacillus amyloliquefaciens* strain	$MnTnHex\text{-}2\text{-}PyP^{5+}$	
SOD3	RM191A *	
SODB *	SOD2m	
TAT-SOD *	Tempol *	

Table 2: SOD-based compounds for potential therapeutic applications between 2012 and 2020[20]

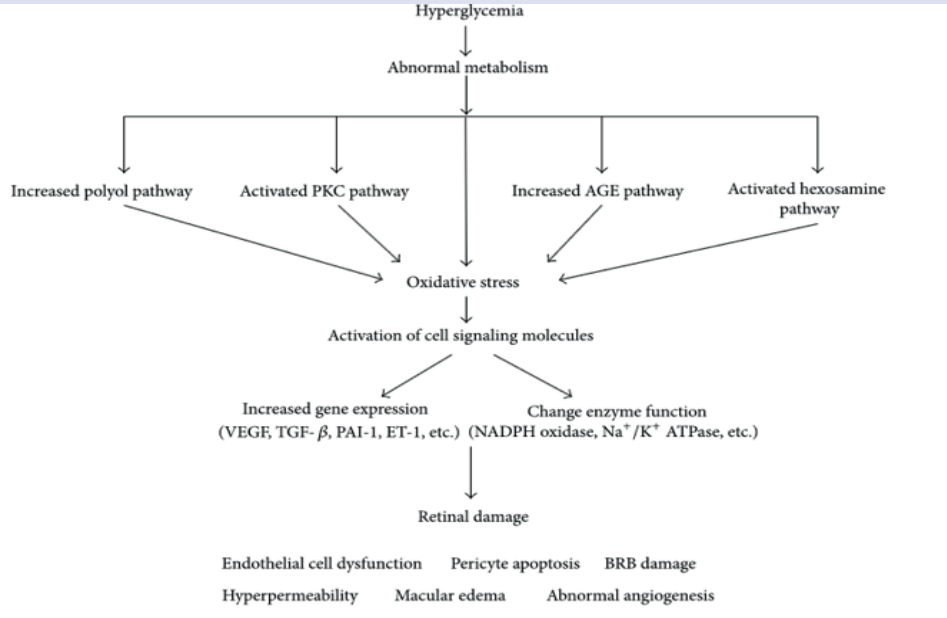

Figure 1: Mechanisms of oxidative stress and diabetic retinopathy[11]

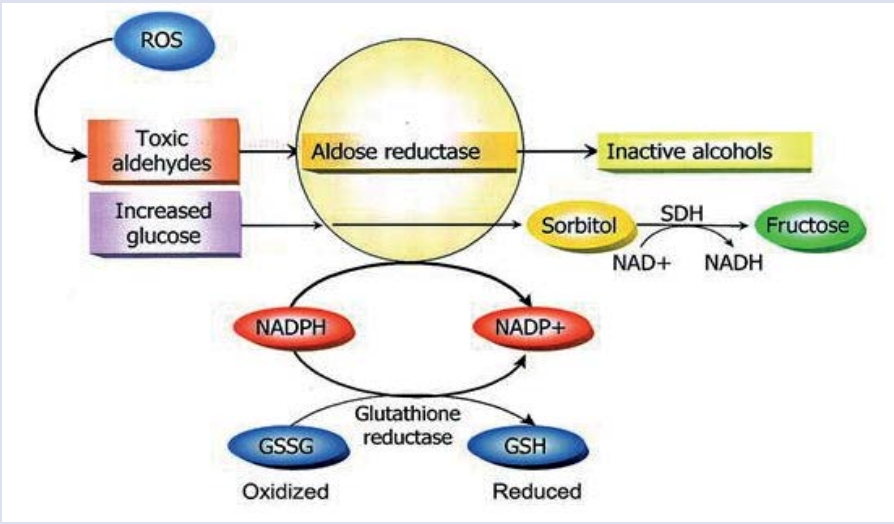

Figure 2: Schematic overview of the polyol pathway[2]

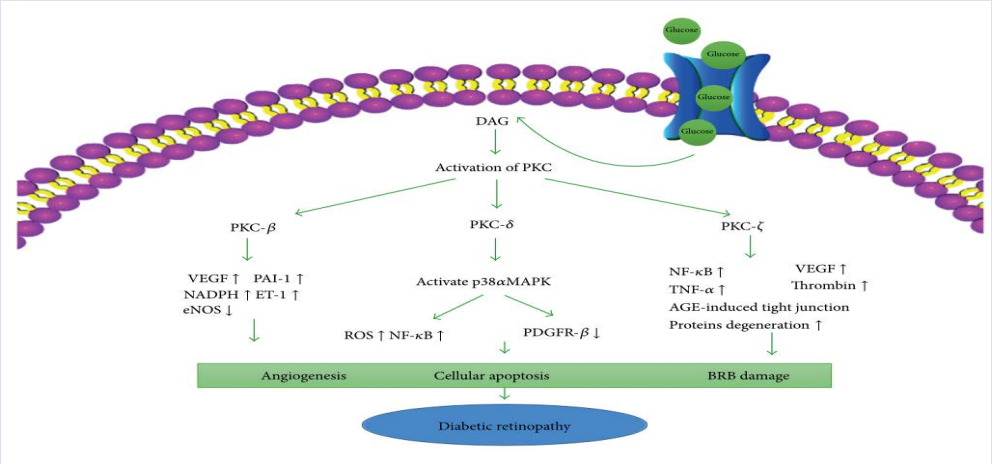

Figure 3: Hyperglycemia-induced activation of three major protein kinase C (PKC) isoforms[2]

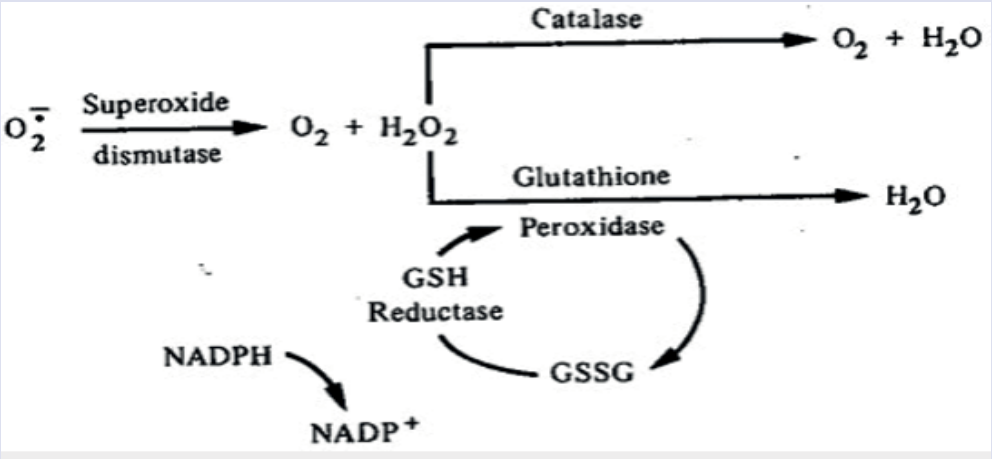

Figure 4: The main antioxidant enzyme system involved in maintaining intracellular redox balance[19]

CONCLUSION

Diabetic retinopathy is a prevalent microvascular complication of diabetes mellitus that threatens vision and can lead to blindness. This condition arises because chronic hyperglycemia increases ROS, activating alternative pathways of glucose metabolism, including the polyol pathway. GSH and SOD are antioxidants that protect the retina from the damaging effects of ROS and help maintain normal cellular redox potential.

The use of melon superoxide dismutase and gliadin (Glisodin®) in ophthalmology related to diabetic retinopathy complications is still very limited. However, research using preparations from other exogenous SOD sources has been carried out and is known to increase antioxidant levels in vitreoretinal tissue and serum blood plasma. Therefore, it is expected to help in the prevention of diabetic retinopathy.

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CONFLICT OF INTEREST

The authors of this review article declare the absence of a potential conflict of interest.

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ETHICAL CLEARANCE

This review article does not require ethical clearance because it does not involve direct experiments on living creatures.

AUTHOR'S CONTRIBUTION

Each author made an equal contribution to this review article.

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