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Role of Antioxidant in the Prevention and Treatment of Type 2 Diabetic Retinopathy

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Abstract: ***Type II Diabetic retinopathy is the prime root of visual detriment among the population caused by the high blood glucose level that affects the back of the eye in which there is reduction in synthesis of various neuroprotective factors includes pigment epithelial-derived factor, brain derived neurotrophic factor, nerve growth factor, somatostatin and interstitial retinol-binding protein in diabetic patients. This review provides an overview of pathways related to diabetic retinopathy and how antioxidant used in prevention, treatment and control of diabetic retinopathy and role of brain derived neurotrophic factor in down regulating oxidative stress. Prior studies have discovered that Type II Diabetic Retinopathy is associated with neurodegeneration and apoptosis that take place in the retina and the hyperglycemia-induced overproduction of reactive oxygen species. Oxidative stress has been regarded as key factor for causing ocular disease and induces local inflammation, mitochondrial and microvascular dysfunction, disruption of blood- retinal barrier, cell apoptosis of retinal capillary cells and downregulation of brain derived neurotrophic factor. Antioxidants supplementation has been related with inhibition of diabetes induced abnormalities of retinal metabolism. Current use of antioxidants to treat ocular manifestations is still poor and recent diabetic retinopathy therapy includes surgery method.***
Keywords: Epigenetics, T2DR, BDNF, oxidative stress, antioxidants

I. INTRODUCTION

Diabetes is a metabolic condition which is characterized by elevation of blood glucose level. One of the major conditions of diabetes is Diabetic Retinopathy (DR) which is the major cause of eye damage. Diabetes is vigorously achieving the potential outbreak in India with more than 62 million diabetic individuals currently diagnosed with this disease (Kaveeshwar and Cornwall 2014). In 2000, India with 31.7 million topped the world followed by China with 20.8 million and United States with 17.7 million peoples suffering from diabetic mellitus (Kumar et al. 2013; Joshi and Parikh 2007). By the end of 1890, characteristics of diabetic retinopathy almost had been completely described, but were not explained. A German ophthalmologist, Julius Hirschberg, had classified diabetic retinopathy into its four stages 1) hemorrhagic form, 2) 'retinitis central is punctu-ate', 3) hemorrhagic glaucoma and 4) retinal infarction (Jörgens 2010). An ophthalmologist Arthur Ballantyne was credited for linking diabetic retinopathy to microvascular retinal dysfunction and alternations (Ballantyne 1943). All these prior discoveries and studies have guided to our current understanding for the pathophysiology and natural progression of Diabetic Retinopathy.

Worldwide, in the most developed countries diabetic retinopathy is one of the most important causes of blindness (Resnikoff and Pascolini, Donatella 2004; Bourne et al. 2013). According to studies done it was recorded that up to 20% of type 2 diabetics have Diabetic Retinopathic lesions at the time of diagnosis, and after 20 years of evolution of the illness >60% of the patients developed diabetic retinopathy and diabetic patients who never undergone an ophthalmoscopic exploration exceeds 30% according to different studies (Vidal-alaball et al. 2019).

There are mainly two stages of diabetic eye damage one of which is Non Proliferative Diabetic Retinopathy and other is Proliferative Diabetic Retinopathy (Robert N. Frank 2004). Non Proliferative Diabetic Retinopathy is also called as macular ischemia as there is the leakage of tiny blood vessels, which make retina swell and blood, cannot reach the macula and makes the vision blurry. Proliferative diabetic retinopathy is called as neovascularization; it is a rife stage of eye damage in diabetic retinopathy, in this stage retina starts growing new blood vessels and these new vessels frequently leak into the vitreous which ultimately lead to detached retina (Pusparajah et al. 2016). Proliferative diabetic retinopathy was first described by Wilhelm Manz in 1876, describing about the retinal adhesions and degeneration of the optic disc (Eshaq et al. 2017). The main reason for irreversible blindness is retinal detachment (Paul and Gardner, Thomas 2002).

There are five classical pathways that were discovered in the development of diabetic complications:

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1) Polyol pathway activation
2) Induction of the hexosamine pathway
3) Activation of angiotensin II pathways
4) Advanced glycosylation end product (AGEs) levels increases in response to the activation of the cell-dependent receptors
5) The activation of protein kinase c (pkc) due to the high glucose-induced peroxide over expression (Brownlee 2001).

Other then these pathways there are also many other aspects which are responsible for complications of diabetes these include : oxidative stress and mitochondrial damage as they induce the production of reactive oxygen species (ROS) and the apoptosis of endothelial cells and pericytes (Tarr et al. 2013). The production of reactive oxygen species (ROS) generally depends on two factors: (a) Mitochondrial oxidative phosphorylation (Golden and Melov 2001) (b) The Nicotinamide Adenine Dinucleotide Phosphate- (NADPH-) Oxidase (Nox) system (Li and Shah 2003). Specifically, epigenetic modifications induces oxidative stress and this can persists for long time i.e. even when the concentration of blood glucose get back to normal level, this develops "metabolic memory" (Intine and Jr 2012). New therapeutic strategies may be provided by the production of scavenging or reducing Reactive Oxygen Species (ROS) by these pathways.

At present, multiple antioxidants have been used in clinical trials, but the results are not clear. In this review, we summarize several of the mechanisms induced by oxidative stress that lowers the BDNF level causing the epigenetic changes leads to T2DR and focus on the latest research into the treatment of the disease using antioxidants.

II. DIABETIC RETINOPATHY

A. *Clinical Feature of Diabetic Retinopathy*

Clinical classification of Diabetic Retinopathy is as follows:

1) Non-proliferative diabetic retinopathy
2) Proliferative diabetic retinopathy

a) *Non – Proliferative Diabetic Retinopathy (NPDR):* At this stage of non- proliferative diabetic retinopathy the lesions remain within the retina and this stage is known as macular ischemia as it includes microaneurysms, splinter haemorrhages, small 'dot and blot' haemorrhages, intraretinal microvascular abnormalities (IRMA) and cotton wool spots. Through the presence of these lesions in various parameters it can be determined that whether the non- proliferative diabetic retinopathy is mild, medium, harsh or very sever (Eshaq et al. 2017). In mild non proliferative diabetic retinopathy there is atleast single microaneurysms and also blot, dot or flam shaped haemorrhages in every four fundus quadrants. In moderate non proliferative diabetic retinopathy there is severity of intraretinal microaneurysms, dot and blot haemorrhages in one to three quadrants. Cotton wool spots and intraretinal microvascular abnormalities are present but are mild (Viswanath 2003). The severe non proliferative diabetic retinopathy can be determined by the presence of at least one of the following: a) venous beading (in atleast two quadrants), b) sever haemorrhages and microaneurysms (in all four quadrants), c) intraretinal microvascular abnormalities (which is severe in atleast one quadrant).

b) *Diabetic Maculopathy:* The macula is the central area of retina which is responsible for all sharp vision. As diabetic retinopathy occurs within and in the region of the macula it is defined as diabetic maculopathy, which results in significant visual impairment. The diabetic retinal changes occur due to pathology appearing at the microvascular part of retina which includes dilatation of the capillaries, destruction of the walls of capillary and closure of the capillaries that result in hypoxia and micro-infarcts (Viswanath 2003).

c) *Proliferative Diabetic Retinopathy (PDR):* The retina is the film at the back of eye and the tiny blood vessels are capillaries, these growing blood vessels are very delicate and bleed easily. Micro- vascular pathology including closure of capillaries in retina leads to hypoxia of tissue that leads to discharge of vasoproliferative factors which arouse new blood vessel formation, these new vessels mounting on retina are known as neovascularization elsewhere (NVE) and those vessels on optic disc are called neovascularization of the disc (NVD). These new growing blood vessels bleed and produce haemorrhage into vitreous in diabetic condition that lead to the detachment of retina (Paul and Gardner, Thomas 2002).

d) *Advanced Proliferative Diabetic Retinopathy:* The progression of proliferative diabetic retinopathy can lead eventually to fractional retinal detachment, which may or may not engage the macula. Vitreous haemorrhage might need B-scan ultra-sonography to resolve if a fractional or rhegmatogenous (retinal break or hole) retinal detachment exists. Neovascularisation of the frontal segment of the eye may cause incurable painful blindness due to neovascular glaucoma. Diabetics are at extensively increased risk of cataract. Measurement of visual acuity should have to be done every year and patients with vision imperfection of less than 6/18 must have to take full eye examination.

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B. Development and Progression of Diabetic Retinopathy

Diabetic Retinopathy (DR) is a polygenic disease, characterized by hyperglycemia, micro inflammation, microvascular damage, increased vascular permeability, leukostasis, vascular occlusion, general neurodegeneration and local ischemia. Due to continual hyperglycemia condition there induces imbalance of cellular metabolism including excessive oxidation of glucose, production of Reactive Oxygen Species (ROS). There is activation of local inflammation because of oxidative stress and endothelial cell death occurs. Hyperglycemic condition causes endothelial cell apoptosis, necrosis, and mitosis which direct to microvascular dysfunction and local inflammation in the retina, which promote blindness. So, formation of inflammation, Reactive Oxygen Species and cell death form a roguish (vicious) cycle, promoting the development of Diabetic Retinopathy (Wu et al. 2018).

In this review, we focused on the increased oxidative stress, which occurs to the activation of polyol pathway which leads to sorbitol accumulation, production of AGEs, activation of the PKC pathway, inflammation, and cell death.

III. DIABETIC RETINOPATHY IN RELATION WITH HYPERGLYCEMIA

The most metabolically active tissue which is easily affected by diabetes is retina. Diabetes is a chronic (life-long) condition, and retinopathy is a time dependent apathetic complexity, thus the retina is repetitively expose to high level of glucose. Hyperglycemic condition produces high levels of methylglyoxal due to enhanced level of glycolysis. Due to the elevated level of the methylglyoxal, matrix metalloproteinases get activated which may further assist in vascular permeability by relating proteolytic degradation of rigid junction proteins such as occludin , thus leading the increased leakage of fluid in surrounding retinal tissue leading to macular edema and vision loss (Kim et al. 2012). It has been considered that hyperglycemia is the first trigger in the role of pathogenesis which lead to diabetic complication due to which there is activation of many pathways and increase of oxidative stress by various mechanisms. Inflammation, oxidative stress and hypoxia-ischemia are the three major hyperglycemia-induced pathologic conditions that are responsible for retinal neuronal damage.

IV. BDNF IN RELATION WITH HYPERGLYCEMIA AND OXIDATIVE STRESS

Brain Derived Neurotrophic Factor (BDNF) is an element of the neurotrophin family, which consist of nerve growth factor, neurotrophin-4/5 (NT-4/5), and neurotrophin-3 (NT-3) (Verge et al. 2014). The function of BDNF is well recognized in neural growth, cell differentiation (maturation), maintenance of target neurons and synaptic connectivity and also its involvement have been seen in synaptic plasticity of brain function, such as memory and learning (Leibrock 1989 ; Barde 1991). Neurotrophin symbolize a family of functionally and structurally associated growth factors that include BDNF and its activation depend upon binding to its receptor i.e. the protein tyrosine kinase receptor (TrkB) which is involved in functional processes of the brain like memory formation, and neuronal connectivity and it also promotes the development of immature neurons and boost the survival of adult neurons (Łukasz and Drzewin 2012). The location of bdnf gene is in a region of 11 chromosome which is the short (p) arm of chromosome 11 at position 14.1 (cytogenetic Location: 11p14.1) the human BDNF has a complicated gene structure, inclosing of 11 exons (I–V, Vh, VI-VIII, VIIIh, IX), among which nine exons (exon I–VII, IX) contain functional promoters. Studies on human suggested the role of BDNF in glucose metabolism and its pathogenic role in the progression of type 2 diabetes mellitus (T2DM). BDNF levels in human serum were significantly found lower in patients with advanced T2DM as compared to normal patients (Fujinami et al. 2008) .

Through the studies it has been demonstrated, at initial stages of Diabetic Retinopathy (DR), specific retinal ganglion cells (RGCs) go through apoptosis and neurodegeneration of retinal is likely to be related with a lack of Brain Derived Neurotrophic Factor (BDNF) (Fernyhough et al. 2003). BDNF plays a critical role in for cells of photoreceptor and for the repair mechanism of retina and optic nerve, it is also expressed in specific retinal ganglion cells (RGCs) and muller glia in the retina (Seki et al. 2003). BDNF support the survival of injured RGCs and also help in regeneration of the nerve fiber (Mey and Thanos 1993 ; Mercedes et al. 1996). Furthermore, studies also show the role of BDNF in promoting the survival of retinal interneurons and are essential for establishing relations between phenotypes and synaptic relations in the developing retina (Guenther and Kohler 2004). BDNF has been reported to restrain neuroretinal cell death under conditions of cardiac ischemia, and to hold back apoptosis in rat RGCs at initial stages of DR (Seigel et al. 2000).

Recent studies are focusing on significant association between elevated blood glucose and low plasma BDNF in type 2 diabetic retinopathy (T2DM) (Krabbe and Nielsen 2007) . Moreover, it has been studied that elevated level of glucose has the negative effect on the production of BDNF from the brain (Krabbe and Nielsen 2007) . It has also been studied that in the brain of T2DR animal models the reduced serum levels of BDNF remain consistent. For an example, acutely decreased mRNA and protein expression of BDNF was found in the hippocampus or cortex of type 2 diabetic db/db mice and in diabetic rats (Krabbe and Nielsen 2007 ;

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Kumari et al. 2018). Low levels of BDNF may accompany impaired glucose metabolism, and decreased *BDNF* may be a pathogenetic factor involved in T2DM (Krabbe and Nielsen 2007 ; Fujinami et al. 2008). The role of BDNF is found to inhibit oxidative stress-induced microglial activation hence, prevents microglia-mediated down regulation of antioxidant enzymes. Also, decrease in BDNF-mediated intracellular cAMP signaling is directly interconnected with upregulated apoptotic signaling in cells, hence confirm the protective role of BDNF and its downstream cAMP-activated targets in keeping a check on neuronal apoptosis (Boutahar et al. 2010).

V. DIFFERENT CAUSES OF DIABETIC RETINOPATHY

A. Oxidative Stress

"Oxidative stress" refers to the state in which there is a severe disparity between the production of an antioxidant defense, oxidants (both reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to tissue damage (Ro et al. 2001). Major members of the Reactive Oxygen Species group are hydroxyl radical, superoxide, and peroxy radical. Main members of the Reactive Nitrogen Species group are peroxynitrite, nitric oxide and their derivatives. For host defense mechanisms oxidative reactions are essential which is mediated by macrophages, neutrophils, and many other cells of the immune system. However, the overproduction of oxidants causes tissue injury and cell death. In regular conditions, antioxidants are there in tissues to counterbalance free radicals and prevent extreme oxidative stress (Halliwell 1996).

Due to the hypermetabolic state the retina is susceptible to oxidative stress (Kagan, E 1973) and the markers levels for oxidative stress are associated with the severity of Diabetic Retinopathy (M.Elizabeth hartnett, et 2000). Due to the pathogenesis of diabetic complications many of different mechanisms including increased superoxide production/decreased scavenging, auto oxidation of glucose, polyol pathway activation and protein kinase C pathway activation, and increased formation of advanced glycation end products leads to increase in oxidative stress (Hamada et al. 2009). Through experiments, it has been demonstrated that the degeneration of retinal capillaries in case of diabetes can be reduced by antioxidant therapy via activation of nuclear factor-κB (NF-κB) and caspase-3, this indicate that oxidative stress plays significant role in apoptosis of retinal capillary (Kowluru and Koppolu 2002 ; Kowluru et al. 2003). Furthermore, it has been reported that due to dysfunction of cone and rod, photoreceptors is thought to contribute to the development of neovascularization and retinal hypoxia (Du et al. 2013 ; Berkowitz et al. 2015). Patients with diabetes and the outer retinal degenerative disorder retinitis pigmentosa have reduced risk of the development of pre-proliferative Diabetic Retinopathy (Arden, 2001 ; Arden et al., 1998). It has been demonstrated that, in the retina of rhodopsin knockout mice with diabetes, it present to have minor vascular attenuation than that of nondiabetic counterparts (Gooyer et al. 2006), the reason behind this may be the failure of rod photoreceptors during retinitis pigmentosa which leads to a final reduction in usage of oxygen by the retina. Thus, it may counteract the exacerbation of hypoxia during T2DR, thus defending the microvasculature from pathogenic changes.

It has been also identified that oxidative stress is responsible for down-regulation of the expression of an enzyme dimethylarginine-dimethylaminohydrolase during hyperglycemic condition; this enzyme is known to be responsible for the metabolism of unbalanced dimethylarginine, a potent inhibitor of endothelial nitric oxide synthase. Hence, the decrease in production of nitric oxide due to the upregulation of assymmetric dimethylarginine induced with oxidative stress and successive downregulation of endothelial nitric oxide synthase. Moreover, the small amount of nitric oxide produced by other isoforms of nitric oxide synthase or by other pathways is utilize in a combination reaction with superoxide radicals (produced during hyperglycemia induced mitochondrial dysfunction) to produce peroxynitrite, a highly reactive species, thus further rising oxidative stress induced damage, besides rendering the body devoid of nitric oxide, a potent vasodilator.

Hyperglycemia-induced endothelial injury can produce reactive nitrogen species through the activation of arginase, leading to disruption of the nitroso-redox balance Finally, increased levels of nitrogen species, including NO and peroxynitrite, promote leukocyte adhesion to retinal vessels, BRB breakdown, and RPE damage (Leal et al. 2007 ; Yuan et al. 2009).

B. Different Mechanisms Underlying Diabetic Retinopathy Due To the Role of Oxidative Stress

Diabetic Retinopathy development is a complex pathological process. Though the mechanisms underlying this have not been completely elucidated, oxidative stress was shown to represent a key factor in this process (Madsen-bouterse et al. 2010) . Experimental and clinical studies demonstrated that the chief factor that leads to pathogenesis of diabetic complications is hyperglycemic condition. (Cade 2008). Oxidative stress not only can damage cell membrane integrity but also (Bonnefont-rousselot 2002), inducing apoptosis, barrier damage and microvascular damage, and finally leading to development of Diabetic Retinopathy.

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1) *Polyol Pathway Activation:* Activation of polyol pathway represents the processes which is been observed under the hyperglycemia-induced oxidative stress conditions during Diabetic Retinopathy (DR) pathogenesis, and this pathway is also known as the sorbitol-aldose reductase pathway (Lorenzi 2007 ; Altmann and Schmidt 2018). At this point, glucose is reduced to sorbitol and afterward oxidized to fructose, with the help of two enzymes: (1) aldose reductase, which converts glucose into sorbitol, (2) sorbitol dehydrogenase, which oxidize sorbitol into fructose (Lorenzi 2007). Aldose reductase and sorbitol dehydrogenase need nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADPH) to convert glucose into fructose (Dunlop 2000). There is regeneration of glutathione (GSH), and an intracellular antioxidant due to the decrease levels of NADPH and activity of polyol pathway increases under hyperglycemic condition (Lorenzi 2007). Due to the over activation of the polyol pathway there is accumulation of Reactive Oxygen Species, which induce oxidative stress in cells. Due to the physiological conditions, hexokinase goes back to the glycolytic pathway by converting fructose into fructose-6-phosphate through phosphorylation. And also, high levels of serum glucose lead to an imbalance between glycolysis and the glycogenesis pathways, causing the accumulation of sorbitol. In a study it was reported that there is imbalance in the process of potential energy reduction process while examining mitochondrial dysfunction during pathogenesis of Diabetic Retinopathy (DR). In diabetes an excess of glucose is converted to sorbitol by enzyme aldose reductase, but this sorbitol cannot penetrate easily into cellular membrane. So, the enzyme sorbitol dehydrogenase catalyze one part of sorbitol molecule which leads to the oxidation of fructose, which is difficult to process further (Schmidt et al. 2005). Therefore, fructose and sorbitol accumulates in cells, which ultimately leads to an increase in edema rupture, membrane permeability damage and osmotic pressure. Taking into consideration, the effect of aldose reductase on retina, there is induction of Diabetic Retinopathic pathogenesis by the activity of aldose reductase simultaneously with the osmotic pressure changes which is caused by the polyhydric alcohol accumulation and by the second step of the sorbitol pathway, in which SDH catalyzes the oxidation of sorbitol to fructose (Netto et al. 2013).56 Due to hypoxia and redox imbalance there is reduction of NAD+ into NADH and increase of intracellular NADH levels, which leads to cell edema, metabolic disorders, microvascular lesion and structural alterations (Ellis et al. 2002).
2) *Hexosamine Pathway Activation:* In this pathway, glucose is converted into fructose-6-phosphate (F6P) by phosphorylation. Fructose-6-phoshapte receives an amino group from glutamine which lead to the formation of glucosamine 6-phosphate by fructose-6-phosphate amidotransferase (GFAT) (Jones et al. 2014). Glucosamine-6-phosphate is acetylated and then isomerized to N-acetyl glucosamine-6-phosphate and lastly converted to diphosphate uracil- N-acetyl glucosamine (UDP-GlcNAc), which is able form glycolipids, glycoprotein's and proteoglycans (Buse 2006). Glucosamine can also be directly phosphorylated by hexokinase, that leads to the production of glucosamine 6-phosphate and its conversion to diphosphate uracil- N-acetyl glucosamine (UDP-GlcNAc) (a substrate for post-transcriptional modification of intracellular factors) (Schleicher and Weigert 2000). This hexosamine pathway was noted to arbitrate the toxic effect of Reactive Oxygen Species (ROS) in hyperglycemia (Jones et al. 2014 ; Buse 2006 ; Schleicher and Weigert 2000). In the state of elevated glucose levels, there is production of large amount of Reactive Oxygen Species, this may inhibit the activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), resulting glycolytic products inflow to the hexosamine pathway (Du et al. 2003) . Due to glucosamine there is increased production of H_2O_2 which is produced by activated hexosamine that further results in changes in cell endothelium, an increased oxidation increased, vascular permeability, and angiogenesis. Inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) induces the Advanced Glycation End Product (AGE) pathway activity as well, by interacting with intracellular methylglyoxal, that ultimately lead to the increase in retinal oxidative stress (Beisswenger et al. 2003 ; Brownlee 2005).
3) *Activation of the PKC Pathway:* Protein Kinase C (PKC) has various isoforms which are triggered by (DAG) diacylglycerol. De novo synthesis of diacylglycerol comes mainly from glycolytic intermediates and acylation of glycerol-3-phosphate stepwise. All the novel isoforms of PKC are triggered by DAG ,but chiefly the ß and α isoforms emerge to be involved in diabetes (Koya et al. 1997). In studies, the level of DAG has been found increased in vascular tissue of diabetic related subjects (Das and King 2007) and as well in cultured vascular cells were found to be exposed to high glucose. And also PKC can also be indirectly activated by hyperglycemia through activation of products of polyol pathway and AGE receptors. Through the activation of phospholipase pathways DAG can also be synthesize by growth cytokines, factors, and hormones, like angiotensin II, which is higher in diabetes (Zhang and Gu 2006 ; Malhotra et al. 2001). The activation of PKC can also be done by superoxide, high amounts of nitric oxide (NO) and peroxynitrite (Johnson et al. 2004). By the activation of PKC-*β,* it was shown to provoke the release of nitric oxide, VEGF and ET-1 in endothelial cells, which lead to decrease in blood flow and an increase in the retinal vascular permeability, causing macular edema & activation of PKC-*δ* induces the development of

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Reactive Oxygen Species and activates the MAPK and p38 pathway. Thus, activation of PKC pathway alters nitric oxide production through Endothelial NOS(eNOS) expression, affecting directly vascular quality, permeability and eventually promoting endothelial dysfunction (Wu et al. 2018).

4) *AGE Accumulation:* Hyperglycemia is the starting occurrence in formation of Advanced glycosylation end product (AGEs) as gluco-carbonyl adducts with amino acids (such as lysine) and involves auto-oxidation of glucose to glyoxal. Besides being interaction with a number of proteins and alter their physical properties, AGEs interact with a specific receptor i.e. RAGE to activate PKC-δ and subsequently occurs NADPH Oxidase (Liand Renier 2006). By the activation of PKC- δ , AGEs activates NADPH oxidase in neural (Nitti et al. 2007). The complications of diabetes have evidently demonstrated the vital role of AGE formation through the studies in animals, tissue culture models and patients (Goldin et al. 2006 ; Yan et al. 2007). An important aspect of the receptor for AGE (RAGE) was studied in pathogenesis of Diabetic Retinopathy (Hudson et al. 2001), and also its activation mediate a broad range of biological effects, which includes increase in Reactive Oxygen Species level, cytokine release, and cell function and death alterations. Endothelial dysfunction is caused by AGE and RAGE, when they interact with intracellular protein which is accumulated in the retinal microvessels (Stitt 2003 ; Yamagishi and Matsui 2010) & also in the retina pericyte apoptosis occurs when AGE accumulation increases through the activation of NF-κB (Katagiri et al. 2017). In the bovine retinal capillary pericytes, following the treatment with AGE solution, pericyte apoptosis and a decrease in the antioxidant activity were observed (Katagiri et al. 2017). AGEs triggers the release of VEGF and cytokines that affect vascular endothelial permeability and self-regulation and induction of inflammation takes place.

5) *Angiotensin II Induces Retinal Oxidative Damage:* Angiotensin II (ANG-II) is the result of Renin-Angiotensin System (RAS) which regulates the systemic and local blood pressures (Funatsu and Yamashita 2003). ANG-II plays fundamental roles in both diabetes pathogenesis and atherosclerosis (Chu and Leung 2009 ; Jr et al. 2008 ; Wu and Li, 2017). So, during Diabetic Retinopathy pathogenesis, ANG-II molecule induce vasoconstriction, oxidative stress, inflammation, cellular dysfunctions, fibrosis, and angiogenesis (Stoschitzky and Williams 1998). Moreover, it can activate NADPH enzyme levels, thus mounting the production of Reactive Oxygen Species and directly damage endothelial cells (Seagle et al. 2006 ; Kowluru 2005). Earlier it was reported that ANG-II induce the generation of peroxynitrite in vascular endothelial cells and promote activation of Poly (ADP-ribose) polymerase (PARP) signaling, which further activates NF-κB and releases many inflammatory cytokines, that damages endothelial cell (Dijk et al. 2016 ; Cai et al. 2017). Effects of these ANG-II can be prevented by the using inhibitors of NADPH Oxidase (Lai et al. 2016 ; Drummond and Sobey 2014).

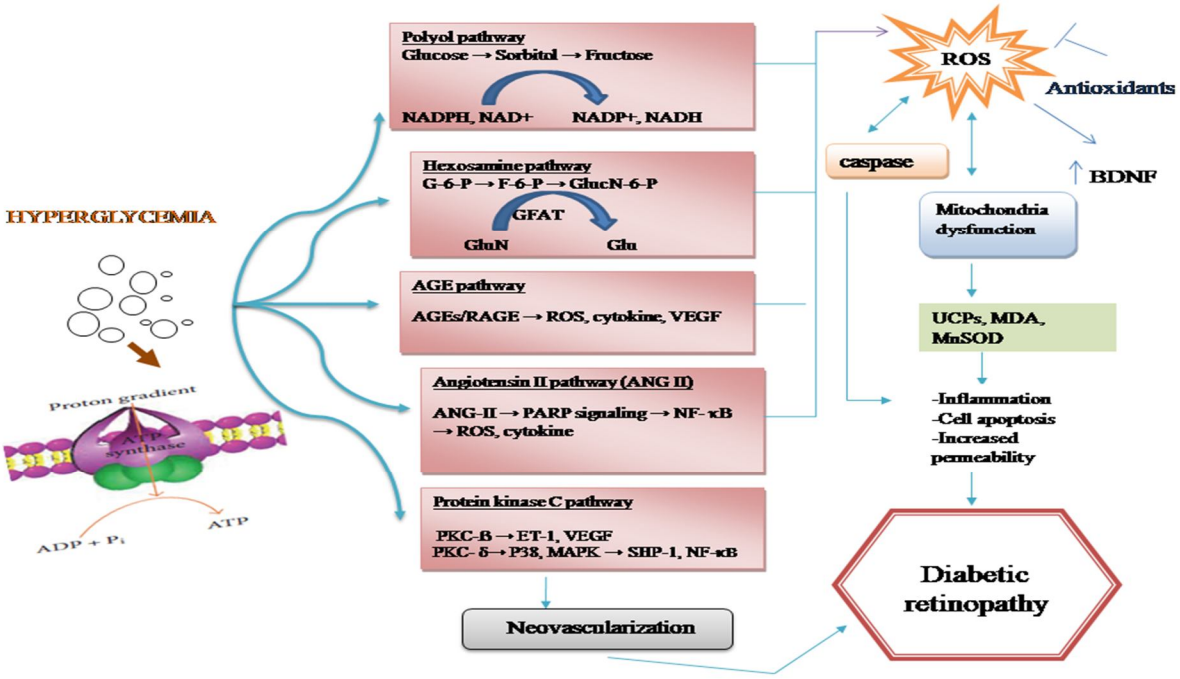


Figure 1: Increased oxidative stress induced by hyperglycemia that is implicated in pathogenesis of diabetic retinopathy. (Wu et al. 2018)

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C. Epigenetic Modifications in the Oxidative Stress Related Pathogenesis of Diabetic Retinopathy

Epigenetic is currently described as the study of changes in gene expression that occur not by changing the DNA sequence, but by modifying DNA methylation and remodeling chromatin. In recent years, major advances in the understanding of epigenetic mechanisms have established them as key players in several cellular processes including cell differentiation, aging, DNA replication, and repair (Mohn and Schu 2009 ; Calvanese et al. 2009 ; Huertas et al., 2009).

After the extension of an elevated glucose level, the pathogenesis of Type II Diabetic Retinopathy continues by a phenomenon which is known as metabolic memory. Through researches it has been founded that one of the most important factors which plays crucial role in the development of Type II Diabetic Retinopathy is epigenetic modifications. Environmental factors, disease progression, lifestyle, and age influence epigenetic changes; DNA methylation, histone modification, and the effects of miRNAs and sirtuin proteins (SIRTs) are considered the major epigenetic modifications.

1) *DNA Methylation:* In DNA methylation there is addition of a methyl group on 5 position of cytosine residues of the cluster of CpG Island (CpG dinucleotides), which is the regulatory region of most genes & typically linked with transcriptional repression (Deaton and Bird 2011 ; Williams et al. 2011). In the methylation process, there occurs the inadvertent changes due to the exposure to different environment and adaption of other life styles, and these changes can be passed on for multiple generations. In the process of methylation, the enzyme DNA (cytosine-5) methyltransferase (Dnmts) catalyses the reaction and convert cytosine 5 methyl to 5-methylcytosine (5mc) and 5mC is converted to 5-hydroxymethylcytosine (5hmC) is by Ten-eleven-translocation enzymes (TETs) (Tahiliani 2012 ; Iyer et al. 2009) , this makes these enzymes the future targets of pharmacological parameter. Increased DNA methylation at the promoter region of the peroxisome proliferator-activated receptor γ coactivator 1-α in the pancreatic islets is shown to play a main role in controlling mitochondrial genes (Ling et al. 2008). In some studies it has been shown, in case of diabetes hyper methylation of CpG sites at the regulatory region of DNA polymerase gamma affects its binding to the mtDNA, and this compromise the transcriptional activity resulting in lower copy number (Tewari et al. 2012). And in some experimental studies, hyperglycemic induction is associated with hypermethylation or hypomethylation of the promoter region in some genes that play critical roles in Type II Diabetic Retinopathy development. For example, research shows that a hyperglycemic milieu can alter the methylation status of the Matrix metallopeptidase (MMP-9) promoter, and the regulation of retinal MMP- 9 promoter hypomethylation can prevent mitochondrial damage and the development of DR (Kowluru et al. 2016). Therefore, DNA methylation is important in the process of DR and metabolic memory.
2) *Histone Modification:* Pattern of gene expression is controlled by chromatin; which is a complex structure of nucleic acid and histones. DNA is wrapped up by histones, a tetrameric structure is formed by histone 2A and B (H2A and H2B), H3 and H4 which is known as the nucleosome (Richmond et al. 1997).99 In spite of sophisticated DNA wrapping, histones N-terminal remains exposed for post-translational modifications, and this exposed N- terminal can be further methylated, phosphorylated and acetylated. The chromatin structure is altered by histone modification which directly affects transcription factors binding, and it can control the particular type of gene expression in a selective tissue by acting like switch to control activity of gene (Zhong and Kowluru 2011; Sawan et al. 2008 ; Berger, 2007). Alteration of gene expression by histone modifications causes the risk of disease, and this process is homeostatically balanced by groups of cellular enzymes that add or remove methyl or an acetyl group. The histone acetylation occurs at lysine residues, while the lysine methylation is associated with gene repression or activation (Kouzarides 2007 ; Martin and Zhang 2005). Enzymes that are involved in acetylation process are histone deacetylases and histone acetyltransferases that can add or remove acetyl groups. Excess activity of histone acetyltransferase result in hyperacetylation, that promote the transcription factors binding and RNA polymerases to the DNA template (Wegner et al. 2014). There is confirmation that, the activity of histone acetyltransferase is reduced and the activity and transcripts of histone deacetylases of histone H3 increased in rats with STZ-induced diabetes (Zhong and Kowluru 2010). In research, it has been shown that in high-glucose cultured endothelial cells of retina, histone H3 modification occurs at lysine 9 (H3K9) at the proximal Cox2 promoter bearing the NF-κB binding site which participate in thioredoxin-interacting protein-mediated inflammation (Perrone et al. 2009). Moreover, upregulation of NF- κB subunit p65 can be induced by transient hyperglycemia that acts as mediator of inflammation in diabetes, by means of active histone H3 lysine 4 monomethylation at the promoter region (Brasacchio et al. 2009). Also, in the diabetic condition hypomethylation of H3K9 releases the lysine 9 of H3K9 for acetylation, which facilitate the recruitment of NF- κB (Zhong and Kowluru 2013). Both hydrogen peroxide and hyperglycemia treatment increases the coactivator-associated arginine methyltransferase 1 expression via histone 3 arginine 17 asymmetric de-methylation in Retinal Pigmented Epithelial cells, proposing that oxidative stress-mediated cell destruction is connected with modification of histone (Kim et al. 2014 ; Kim et al. 2015).

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3) *Micro RNAs (mi RNAs):* In addition to histone modifications and DNA methylation, microRNAs (miRNA) also regulate gene expression this miRNA is the small, single stranded noncoding RNAs. They contain 20-24 nucleotides and regulate gene expression posttranscriptionally by interacting to complementary sequences in the 3'untranslated regions of messenger RNAs (Garzon et al. 2009 ; Dykxhoorn et al. 2003). This cleaves mRNA resulting in decreased protein synthesis and expression of the targeted gene. In the progressive diabetes miRNA expression is a predictive factor and in diabetic patients circulating miRNA get altered (Zampetaki et al. 2010). miRNAs can control expression of gene through many other ways, that includes translational repression, de-adenylation and mRNA cleavage, and also miRNAs have quickly emerge as promising target for the growth of novel therapeutics. To aim specific miRNA there are two commonly inspected techniques i.e. anti-mRNA antisense oligodeoxyribonucleotide and miRNA mimics. Double-stranded miRNA mimics and anti-mRNA antisense oligodeoxyribonucleotide are the two commonly investigated techniques to target specific miRNA. In the pathogenetic mechanism of diseases miRNAs have a exact and definite target, miRNA-based therapy have benefit that they target various genes that are involved in the process of similar pathway (Caroli et al. 2013). One of the major caveats with the miRNA-based therapy is their delivery, as these modulators must leave the circulatory system to get into the target tissue and should be able to cross blood-retina barrier. The other important issue is their circulatory half-life. The advances in drug delivery techniques, however, could open up the use of miRNAs for diabetic retinopathy.

4) *SIRTs:* Sirtuin (SIRTs) is homologs of silent information regulator 2 in higher eukaryotic organisms. They are involved in epigenetic modifications of histone protein deacetylation and nonhistone protein deacetylation, which are involved in the mechanisms of vascular dysfunction related to cardiovascular disease, aging, diabetes, and other metabolic diseases (Onofrio et al. 2015). Mammals have seven SIRTs (SIRT1–7) that depends on a cofactor NAD+; in which SIRT1 and SIRT3 are closely linked with diabetes and complications related to it. The fact which is chiefly true for SIRT1 (Onofrio et al. 2015), (Abdefg et al. 2011), is that, it regulates responses of oxidative stress and apoptosis of RPE cell through the deacetylation of cytoplasmic p53 (Bhattacharya et al. 2012). In recent study it has been demonstrated that the activity of SIRT1 decreases in diabetic retinas (Kubota et al. 2011) and additionally overexpression of SIRT1 protects pancreatic β-cells by inhibiting the NF-κB pathway through de-acetylation of p65 (Lee et al. 2009). In experiments it was noted that, in cultured cells of mammalian, SIRT1 gets activated in retort to energy stress and increased oxidative stress. Evidences also show that SIRT1 is strongly related to redox modulation because its activity depends on intracellular NAD+ (Dioum et al. 2014). Moreover, exendin- 4 reduce the number of cells of retina and the production of Reactive Oxygen Species by up-regulating the expression of SIRT1 and SIRT3 in the retinas of early-stage diabetic rats (Zeng et al. 2016).

D. Mitochondrial Electron Transport Chain

The reason behind disruption of normal mitochondrial function and elevation in superoxide production is hyperglycemia. The mitochondrial dysfunction occurs due to the increase in hyperglycemia derived electron donors mainly from citric acid cycle (NADH and $FADH_2$). They increases the e^- flow through electron transport chain (ETC) complexes and also the protons efflux from mitochondrial matrix across the inner mitochondrial membrane by complexes I, III, and IV.

This can lead to a significant increase in potential of mitochondrial membrane and the preferable inhibition of electron flow through complex III. This inhibition disrupts normal electron flow of ETC and promote the leakage of electrons leading to the formation of superoxide (Paradies et al. 2001). Thus the increase in superoxide formation leads to damage of oxidative mitochondrial and cellular lipids, nucleic acids, and proteins which contribute greatly to the pathology of hyperglycemic/diabetic state. These destructive damages are proliferated by the fact that free-radical defense mechanisms such as (SOD) superoxide dismutase, catalase, glutathione peroxidase, and levels of the intracellular antioxidant GSH are also substantially compromised during diabetes (Kowluru and Chan 2007) . The primary role of mitochondrial ROS production in diabetes-induced oxidative damage in the retina has been determined by recent studies on transgenic mice that over express mitochondrial SOD.

Increased production of superoxide may induces sustained harmful effects by destructing mitochondrial DNA (mtDNA)and proteins that result in altered Electron Transport Chain subunits, in addition this could produce larger amount of superoxide (Houten et al. 2006 ; Stuart and Brown 2006). Further, nitric oxide react with superoxide and generate a powerful oxidative agent i.e. peroxynitrite which have a long mean life cycle, peroxynitrite can directly stimulate lipid peroxidation, inactivation of enzymes and turn on cascades of events that results in viability of the cell and DNA damage (Radi et al. 2002 ; Schreiber et al. 2006 ; Pacher et al., 2007). In studies, it has been shown that due to diabetes there is increase in levels of mitochondrial superoxide and peroxynitrite level in retinal cells and thus the increased oxidative stress is involved in the development of type II diabetic retinopathy (A et al. 1997 ; KOWLURU 2005 ; Kowluru and Kanwar, 2009; Kowluru et al. 2003). Thus, due to the elevation in oxidative stress mitochondrial

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dysfunction occurs and their membrane potentials gets impaired, and the activity of complex III of the ETC system is impaired in the retina and capillary cells (Mohammad and Kowluru 2010). Studies in animal models of diabetic retinopathy has been done which proves that, the supplementation of anti-oxidants inhibits oxidative stress and the development of retinopathy (Kowluru and Odenbach 2004 ; Kowluru and Kanwar, Mamta 2015). There is a classical antioxidant defense system in mammalian cells that help to neutralize free radicals and to converse the cellular redox homeostasis; this defense system is made up of various cellular and mitochondrial enzymes that includes superoxide glutathione peroxidase, reductase and scavenging enzymes. Superoxide radicals immediately cannot cross membranes, but (MnSOD) manganese superoxide dismutase which is a superoxide scavenging enzyme, converts intramitochondrial superoxide to hydrogen peroxide that can diffuse through mitochondria. In the diabetic condition, retina experience weaken antioxidant defense system; the activities of antioxidant defense enzymes-MnSOD, catalase and glutathione peroxidase are decreased, and the levels of glutathione are below normal (A et al. 1997).

1) *Mitochondrial Dysfunction:* The primary source of cellular energy is mitochondria, whose main function includes metabolic processes and respiration and their main function includes the production of cell metabolism control, adenosine triphosphate (ATP) production, and apoptosis regulation (Schef 2001 ; Santos et al. 2012) and their dysfunction harshly affects tissue homeostasis. Under hyperglycemic conditions, Reactive Oxygen Species is overproduced in the retina, leading to an increase in oxidative processes, which may escort to the apoptosis of retinal capillary cell (Bouterse et al. 2010 ; Mohammad and A 2011). Due to this increased oxidative stress increase during hyperglycemic condition, the structure and function of mitochondria gets damaged (Bouterse et al. 2010). Mitochondria are the major source for the production of Reactive Oxygen Species, they have their own DNA, and this DNA is exceptionally circular and small with only 16.2kb. Nuclear DNA is packed into nucleosomes, but mitochondrial DNA (mtDNA) lacks histones and is packed as nucleoid-like structures (Chen and Butow 2005 ; Kucej et al. 2008). This 'naked' DNA, is more susceptible to damage from defects generated by the electron transport due to its close proximity to the ROS-generating electron transport chain (Kucej et al. 2008 ; Wanrooij and Falkenberg 2010). Due to diabetes retinal mitochondrial DNA (mtDNA) damages; although the retina tries to overcome damage to its mtDNA by stimulating enzymes for DNA repair, that remain deficient in the mitochondria (Bouterse et al. 2010). Mitochondrial DNA conceal only 13 subunits of the electron transport system among which seven from complex I (ND1, ND2, ND3, ND4, ND4L, ND5, and ND6), one from complex III (cytochrome b), three from complex IV (COI, COII and COIII), and two from complex V (subunit 6 and subunit 8) (Johannsen and Ravussin 2009). mtDNA is very small in size and does not contain histones; instead this DNA is covered with proteins, mainly the mitochondrial transcriptional factor A (TFAM), to form nucleoid (Ohgaki et al. 2007). In diabetic retinopathy, the binding of TFAM to a nonspecific region of mtDNA is decreased resulting in decreased levels of mtDNA-encoded proteins, and damaging the mtDNA (Santos et al. 2012 ; Santos and Kowluru 2013). Since posttranslational modification of histones affects nDNA transcription, it is plausible that such changes in TFAM structure might affect mtDNA transcription. This suggests that by maintaining mitochondrial homeostasis by attenuating epigenetic changes using pharmaceutical or molecular means could help delay further progression of diabetic retinopathy.

VI. ANTIOXIDANT TREATMENT AND DIABETIC RETINOPATHY

In the above sections, we have discussed that the oxidative stress plays a fundamental role in the development of T2DR. Consequently, it is assumed that antioxidants works for inhibition of abnormal metabolism and slow Diabetic Retinopathy progression by inhibiting the production of Reactive Oxygen Species and neutralizing free radicals or augmenting the antioxidant defense system. Therefore, these factors are targets in the treatment of Diabetic Retinopathy.

1) *Vitamins:* After studies it has been stated that vitamins C and E can protect against the development of Type II Diabetic Retinopathy by scavenging free radicals, reducing the production of Reactive Oxygen Species, and preventing lipid peroxidation (Pazdro and Burgess 2010 ; Jariyapongskul et al. 2007). Therefore, supplementation with vitamins C and E is thought to be helpful in the treatment of DR. Vitamin C can improve endothelial dysfunction in diabetes and weaken leukocyte adhesion in retinal vessels in diabetic rats (Jariyapongskul et al. 2007). Vitamin E inhibits the PKC pathway in diabetes; the PKC pathway induces a decrease of retinal blood flow, resulting in retinopathy (Kunisaki et al. 1995). Recently, vitamin D has been in consideration as important vitamin in the development of T2DR. In research it has been noticed that vitamin D deficiency is very common in type II diabetes, and there is an increased risk of retinopathy in diabetic patients with acute vitamin D deficiency (Alcubierre et al. 2015).
2) *Green tea:* Green tea, which is rich in polyphenols, is thought to have effective antioxidative, anti-inflammatory and anticarcinogenic properties (Wang et al. 2014 ; Kumar and Gupta, Suresh 2012).150, 151 Green tea supplementation in diabetic rats increases the level of glutathione (GSH) and the activities of superoxide dismutase (SOD) and catalase, reduces the

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expression of VEGF and TNF-α, and protects retinal vessels from angiogenesis and retinal endothelial cells from apoptosis (Kumar and Gupta, Suresh 2012). These results specify the beneficiary effects of green tea in the treatment of T2DR.

3) *MnSOD (Manganese Superoxide Dismutase)*: Is the most important superoxide scavenger, so by direct activation of this superoxide is a vital approach/ route to prevent mitochondria dysfunction in this organelle. Research shows that by the administration of lipoic acid, a co-factor for some of the enzymes including MnSOD, prevents the apoptosis of retinal capillary cells, the advancement of retinopathy in diabetic rats and nullify mitochondrial dysfunction (Kowluru et al. 2006 ; Kowluru and Odenbach 2004). In other studies shows that lipoic acid delay retinal blood barrier breakdown, which is a hallmark of Diabetic Retinopathy (Berkowitz et al. 2007). A synthetic mimicry of MnSOD plus MnTBAP prevents hyperglycemia-induced superoxide generation and apoptosis in retinal endothelial cells, and over expression of MnSOD in mice prevent the development of Retinopathy in diabetic mice (Kanwar et al. 2007 ; Kowluru and Kanwar 2009). These studies have suggested that through regulation of MnSOD by pharmacologic or genetic means; have potential to inhibit the progress of retinopathy in diabetic patients.
4) *Troxerutin:* (vitamineP4) is a type of flavonoid which is known for its antioxidant and radio protective properties (Panat et al. 2016). Through the studies its is reported that by the administration of this compound to diabetic suffering animals was found to attenuate VEGF expression and oxidative stress in the retinal eye; but however mechanistic studies were not performed and therefore confirmatory studies are needed to be done for seeing its beneficial effects in prevention of diabetes induced retinal tissue injury (Chung et al. 2012).
5) *Resveratrol (RVT):* (3,4,5- trihydroxystilbene) RVT found in grapes and fruit berries, is a type of natural polyphenolic phytoalexin. It is useful in the treatment of diabetes, neurodegenerative disease and heart related problems (Bola et al. 2014 ; Pangeni et al. 2014).157, 158 According to researches this polyphenolic was found to suppress diabetic- induced oxidative stress, pro-inflammatory cytokines expression, activation of NF-κB and occurrence in the retinal tissues. Moreover, its treatment prevents diabetes induced neuronal cell death, basement membrane thickening and vascular hyper permeability. Thus , it may also improve the retinal nerve function (Farhad ghadiri soufi et al. 2012).

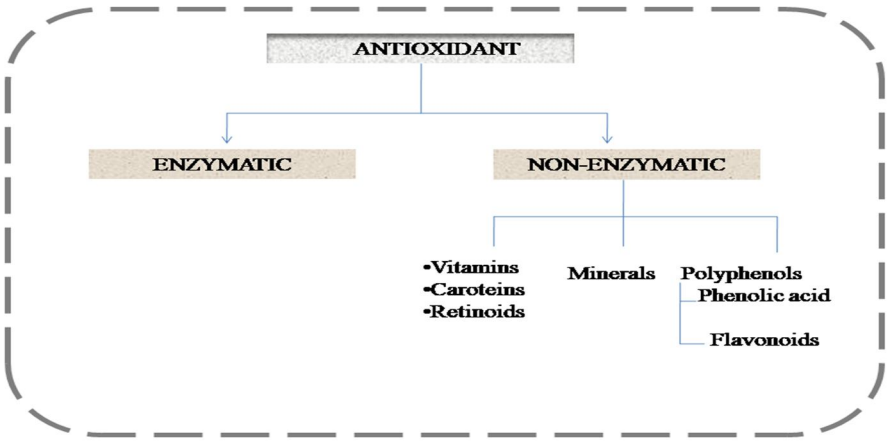


Figure 2: Antioxidants structure classification (Baptista et al. 2010)

VII. CONCLUSIONS

Throughout the studies on T2DR it can be concluded that T2DR remains the main cause of blindness among various age groups in which oxidative stress is a major factor for its development. It has also been considered that BDNF is vital neurotrophin that is required for proper growth, generation and for maintenance of neurons. In this review it has been demonstrated that how under hyperglycemic condition the metabolic changes takes place and lead to the accumulation of ROS production which initiate oxidative stress and hence lower down the BDNF level which causes neuronal degeneration. Thus, neuro protective effects of BDNF were not observed during T2DR. It also includes how oxidative stress causes downregulation of BDNF level causing retinal damage through the activation of different pathways and epigenetic modifications that are involved in pathological process of T2DR. So, to prevent from such pathological processes, inhibitors of these pathways are required and also require the upregulation of BDNF level by

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inhibiting pathological factors caused by hyperglycemic condition hence, lowering or inhibiting the progression of this complication. This review paper concluded that, therapies which prevent superoxide accumulation and maintain mitochondrial homeostasis and protect mtDNA, appears to be the most likely strategies to prevent the development of T2DR. Thus, therapies that could target multiple steps of oxidative stress and mitochondrial damage should provide a hope for the prevention of this multifactorial blinding complication of diabetes. Antioxidants are beneficial for T2DR because they reduce ROS production, neutralize free peroxynitrite, or augment the antioxidant defense system. Furthermore, herbal extracts have received increasing attention for treating DR in recent years, although the mechanisms underlying their mode of action require verification. At present, most of the evidence has been provided by animal experiments, and the clinical therapeutic effects are still not very clear. Thus, more work is needed in the future.

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A. Statement of Interest

None to declare.

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ABBREVIATIONS

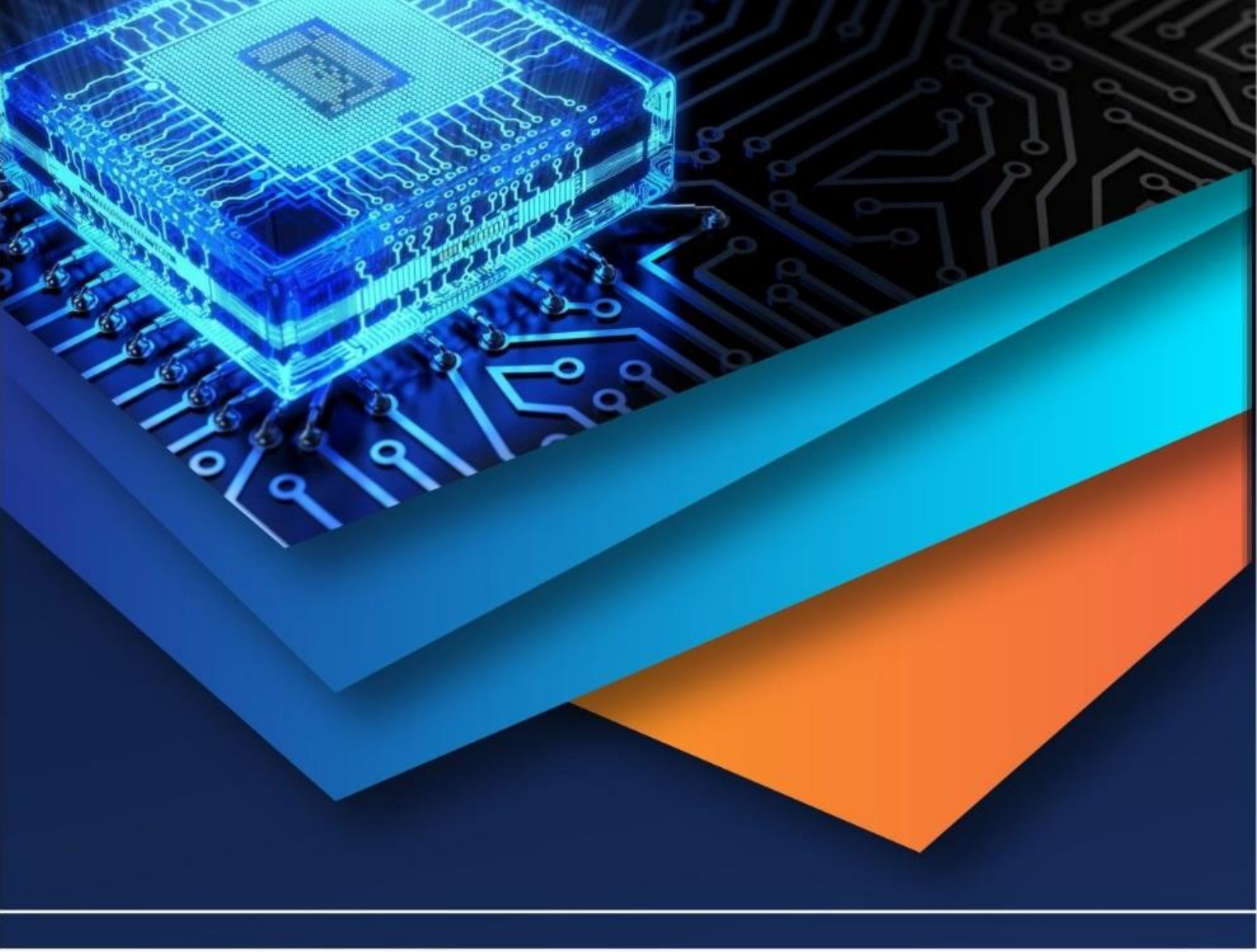
1) ADP: Adenosine diphosphate
2) AGE: Advanced glycation end product
3) ATP: Adenosine triphosphate
4) BDNF: Brain- derived neurotrophic factor
5) ET-1: thromboxane and endothelin-1
6) F6P: fructose-6-phosphate
7) G6P: Glucose -6- Phosphate
8) GFAT: Glutamine- fructose-6-phosphate transaminase 2
9) Glu: Glutamic acid
10) GlucN6P: N-acetylglucosamine 6-phosphate
11) MAPK: Mitogen - activated protein kinases
12) MDA: Malondialdehyde
13) MnSOD: mitochondrial superoxide dismutase
14) NADH: Nicotinamide adenine dinucleotide
15) NADPH: Nicotinamide adenine dinucleotide phosphate
16) NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
17) PARP: Poly(ADP- ribose) Polymerase
18) PKC: Protein kinase C

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19) ROS: Reactive Oxygen Species
20) SHP-1: Tyrosine- protein phosphatase non-receptor type 6/ Src homology region 2 domain containing phosphatase-1
21) UCPs: Uncoupling Proteins
22) VEGF: Vascular Endothelial Growth Factor

Figure 1: Increased oxidative stress induced by hyperglycemia that is implicated in pathogenesis of diabetic retinopathy. The figure illustrate that in hyperglycemic state there is overproduction of ROS with the involvement of various pathways that includes (a) Polyol pathway also known as sorbitol-aldose reductase pathway (b) Hexosamine pathway- There is large production of ROS due to the elevated level of glucose levels, a large amount of ROS is generated, that inhibit GAPDH activity, that results in the entry of glycolytic products back to the hexosamine pathway (c) Activation of the PKC Pathway (d) Advanced glycation end product (e) Angiotensin II Induces Retinal Oxidative Damage.
Figure 2: Antioxidants structure classification. Antioxidants can be derived from dietary foods which include Vitamins A, C, E and carotenoids. Phenols can be found in all plant foods (that contain phenols, phenolic acids and flavonoids).

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