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Antioxidant Status of Human Retinal Pigment Epithelium: A review

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ABSTRACT

Reactive oxygen species (ROS) show both beneficial as well as harmful effects, especially when the level of ROS increased beyond the level of antioxidants it proved harmful to any living system. Oxidative stress (OS) is the imbalance of the level of antioxidants and ROS. The antioxidants are compounds that showed their presence by fighting against ROS. ROS damages various macromolecules such as protein, lipids, carbohydrates, and DNA. An antioxidant such as SOD, CAT, GSH-Px, and GR show their role by mitigating the harmful effects of ROS on the cellular macromolecules. Especially in the retina, the OS plays a vital role in the occurrence of retinopathies. Retinopathy is any impairment in the retina which leads to loss of visual acuity. The declined level of antioxidants leads to oculopathies such as diabetic retinopathy (DR), age-related macular degeneration (AMD), and other macular degenerative diseases. The retina is more susceptible to OS because of the presence of polyunsaturated fatty acid and photooxidative injury. AMD is the leading cause in the world but its occurrence due to OS is poorly understood. Additionally, it is found that the alteration of antioxidants in retinal pigment epithelial cells was observed in *in vitro* and *in vivo* conditions. There is a need to understand the underlying mechanism, either OS is responsible for retinopathies or the disease itself leads to stressful conditions in tissue or cells. In the current review article, we put an attempt to summarize the recent link between OS and retinopathies such as DR and AMD.

Keywords: Reactive Oxygen Species, Oxidative Stress, Retinal Pigment Epithelium, Superoxide Dismutase, Catalase, Glutathione Peroxidase, Glutathione Reductase

INTRODUCTION

1.1 Retinal pigment epithelium

The monolayer retinal pigment epithelial cells (RPECs) are highly polarized cells that are found between photoreceptors and choroids (Panda-Jonas *et al.*, 1996) (see figure 1). Apically oriented microvilli, tight junctions, melanosomes, and a basally positioned nucleus, as well as some basal attachments with the choroid, can all be described as morphologically polarized RPECs (Sundelin *et al.*, 2001). RPECs are important in regular physiology as well as several signaling pathways that are required for normal eyesight. It also helps transfer nutrients from the choroid, serves as a blood-retinal barrier (BRB), and absorbs excess dispersed light to prevent photooxidation (Bok, 1993). They lose their epithelial polarity in pathological settings, causing them to become dedifferentiated, dysfunctional, and eventually perish (Yang *et al.*, 2018). To discover the diagnostic treatment for highly common yet sight-threatening retinal disorders, researchers must first understand the function of oxidative stress (OS) in retinopathies.

1.2 Oxidative stress

The lonely unpaired electrons in the outermost shell of molecules are called reactive oxygen species (ROS) (Sindhi *et al.*, 2013). The ROS is composed of different radicals such as superoxide and non-radicals such as hydrogen peroxide, and ozone (Murphy, 2009), (Bayir, 2005), (Sindhi *et al.*, 2013). Other reactive substances such as ketoamine and ketoaldehyde are also categorized as ROS (Gracy *et al.*, 1999),(Ung *et al.*, 2017). A thorough discussion of the many forms of ROS may be found elsewhere (Beatty *et al.*, 2000), (Held, 2012). ROS including hydrogen peroxide played beneficially as well as harmful effects depending upon its concentration and microenvironment (Ung *et al.*, 2017), (Trakkides *et al.*, 2019). The concept of OS begins from an oxidation-reduction reaction (Beatty *et al.*, 2000). OS is defined as an imbalance of the ratio of ROS generation and antioxidants (Bayir, 2005), (Subrizi *et al.*, 2015),(Ung *et al.*, 2017). Briefly, the beneficial role of ROS can be explained as it showed fundamental cellular functions such as cell proliferation, inflammatory response, apoptotic cascade, specific gene expressions, survival, and migration (Li *et al.*, 2015),(Ung *et al.*, 2017). ROS acts as a secondary messenger for normal cellular homeostasis to maintain signal transduction and cell cycle regulation (Hancock *et al.*, 2001),(Held, 2012),(Ung *et al.*, 2017). The induction and suppression of apoptosis depend upon the intracellular concertation of ROS (Simon *et al.*, 2000), (Ung *et al.*, 2017). Especially in the eye, recent evidence supports that a lower concentration of ROS helped to maintain normal immunity against any sight-threatening condition (Kumar *et al.*, 2013). ROS-mediated response exhibited by macrophages, neutrophils, and microglia defend against pathogenic infection in eye (Kumar *et al.*, 2013).

Despite the beneficial role of ROS, it showed several harmful effects at the cellular and tissue level (Ung *et al.*, 2017). As mentioned earlier ROS like superoxide radicals are highly reactive to surrounding vital cellular macromolecules such as lipids, proteins, nucleic acid (Schieber and Chandel, 2014), (Mateos, 2015) which ultimately leads to oxidative injury such as cell death (Sindhi *et al.*, 2013), (Huang *et al.*, 2014),(Mateos, 2015), (Zhao *et al.*, 2019). Due to cellular damage, the proteins oxidize and accumulated in cells (Sindhi *et al.*, 2013), (Ung *et al.*, 2017), (Mitra, 2020). The ROS-mediated damages to cellular macromolecules such as purines and pyrimidines of DNA are responsible for the aging and other old-age disorders (Ames and Gold, 1991), (Beatty *et al.*, 2000), (Kim *et al.*, 2003).

1.3 Antioxidants

The removal of ROS from the body is very necessary for the survival of organisms (Held, 2012). The antioxidants play a vital role in maintaining ROS (Ung *et al.*, 2017), (Mitra, 2020). Antioxidants are available naturally and also present in the body to fight against the damages caused by ROS (Mitra, 2020). It protects the macromolecules by nullifying the oxidation of cellular macromolecules by neutralizing the free radicals from blood (Young and Woodside, 2001), (Kim and Byzova, 2014), (Mitra, 2020). The chelation, transfer of electrons, and transfer of hydrogen atoms from molecules are different strategies by which the antioxidants nullify the ROS (Foyer and Noctor, 2005), (Møller *et al.*, 2007),(Mitra, 2020).

One way of classifying the antioxidants is natural or synthetic. The natural antioxidants are derived from naturally available foods such as fruits, vegetables, and spices while the Butylated hydroxytoluene (BHT) and Butylated hydroxyanisole (BHA) are considered synthetic antioxidants (Sindhi *et al.*, 2013). Another way of classifying the antioxidants is based on the level

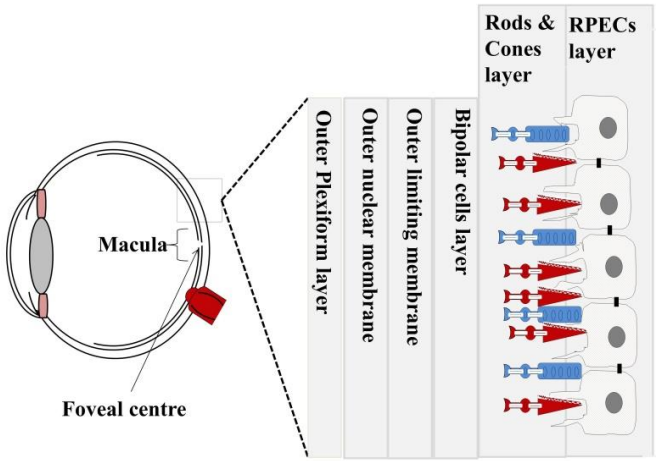

Figure 1: Schematic representation of retinal layers and location of RPECs.

The retina is mainly composed of inner retinal membranes and outer retinal membranes. The outer retinal layers are composed of the outer plexiform layer, outer nuclear membrane, outer limiting membrane, bipolar cells layer, rods-cones cells, and then retinal pigment epithelial cells (RPECs). The RPECs possess tight junctions and rest on Bruch's membrane of choroid thus acting as blood-retinal barriers and performing many other vital functions.

of antioxidant activity. The antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) along with minerals such as Se, Cu, Zn are categorized as the first line of defense mechanisms (Subrizi *et al.*, 2015), (Ung *et al.*, 2017). The antioxidants like glutathione (GSH), vitamin C, albumin, vitamin E, carotenoids, flavonoids are considered the second line of defense mechanism and the third line defense mechanism of antioxidants involving the lipase, protease, DNA repair enzymes, transferases, and methionine sulphoxide reductase (Sindhi *et al.*, 2013), (Subrizi *et al.*, 2015), (Ung *et al.*, 2017). It has been observed that the antioxidants such as SOD, CAT, and GSH-Px are found in retinal tissues like RPECs and photoreceptors (Sen *et al.*, 2002), (Kovacic *et al.*, 2008), (Sjølie *et al.*, 2011), (Ung *et al.*, 2017). The RPECs utilize various strategies among the antioxidant enzyme to protect the cells (Cohen *et al.*, 1994), (Plestina-Borjan *et al.*, 2015). Oxidative injury results due to over ROS-generation or insufficient antioxidants status which further store the degraded cellular molecules like lipids, proteins that suppressed regeneration of light-sensitive cells (Hamilton *et al.*, 2004). So, the antioxidant status showed a very crucial link to the protection of normal vision (Ni *et al.*, 2019). The antioxidants status provides the clue or levels of oxidative injury in any living system. Especially in retinal pigment epithelial cells (RPECs) and neurosensory retina, the first line of the antioxidants is observed (Beatty *et al.*, 2000).

1.4 Oxidative stress and retinopathies

1.4.1 Retinopathy

Any impairment in the retina which leads to loss of normal vision is called retinopathy (Duh *et al.*, 2017). The current understanding of retinopathy suggested that the loss of normal vision due to retinal dysfunctions occurs at various levels of the retina such as abnormal endothelial vasculogenesis, uncontrolled angiogenesis, pericytes apoptosis, altered blood-retinal barrier, fluid leakage, and neuronal cell dysfunctions (Fletcher *et al.*, 2007), (Agarwal *et al.*, 2015), (Ung *et al.*, 2017). The accumulation of H2O2 results in subretinal tissues where the level of antioxidants found diminished due to photooxidative stress (Yamashita *et al.*, 1992), (Trakkides *et al.*, 2019). It is a fact that ROS results from various compartments of cells (Bedard and Krause, 2007). Some habits may contribute to enhancing oxidative injury to OS-sensitive tissues like RPECs (Angulo Daniela, 2015). There are several factors are known to be involved in damaging RPECs such as smoking, altered body mass index, photooxidative stress, and irregular visual cycle activation in RPECs (see figure 3) (Milton *et al.*, 2005), (Ozawa *et al.*, 2012), (Sasaki *et al.*, 2012), (Sui *et al.*, 2013), (Narimatsu *et al.*, 2015), (Kamoshita *et al.*, 2016). Above all, some factors act as very prominent risk factors such as age, genetics, tobacco use, and low antioxidants in diet (Smith *et al.*, 2001), (Ung *et al.*, 2017). Several other factors lead to RPECs dysfunctions such as low antioxidant metallothionein

(Lu *et al.*, 2002), irregular Nrf2 signaling pathway (Cano *et al.*, 2010), and VEGF mediated ROS generation (Monaghan-Benson *et al.*, 2010), (Ung *et al.*, 2017).

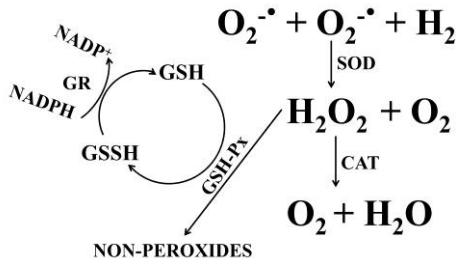

Figure 2: Schematic representation of the antioxidants interplay.

In brief, the superoxide radicals are scavenged by SODs (Li *et al.*, 2015) (Costa *et al.*, 2014) which participate in the generation of comparatively less harmful substances such as H_2O_2 (Guruvayoorappan, 2008). H_2O_2 is further encountered by CAT and GSH-Px. The CAT catalyzes H_2O_2 into water and molecular oxygen (Sajeeth *et al.*, 2011). The GSH-Px acts on H_2O_2, as well as other lipid hydroperoxides, converted into non-peroxide radicals under normal homeostasis. Glutathione and NADPH are utilized as electron donors and acceptors for oxidation-reduction (Weydert and Cullen, 2010). ($O_2^{-\bullet}$- Superoxide radical, H_2O_2-hydrogen peroxide, SOD-superoxide dismutase, CAT-catalase, GR-glutathione reductase, GSH-Px- glutathione peroxidase, GSSG- oxidized glutathione, GSH- reduced glutathione, $NADP^+$-reduced nicotinamide dehydrogenase phosphate, NADPH-oxidised reduced nicotinamide dehydrogenase phosphate).

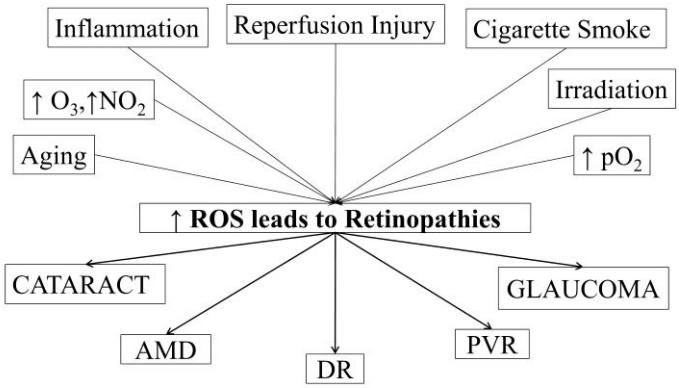

Figure 3: Stimulus for ROS-generation and resultant oculopathies.

Due to abnormal antioxidants and their related homeostasis, there are several reactive oxygen species generated and resulting in physiological responses. There are several stimuli like the higher concentration of harmful ozone, nitrogen dioxides; partial pressure of oxygen, inflammation, reperfusion injury, light irradiation, cigarette smoke, and even aging are responsible for ultimate increased ROS-level and result in several oculopathies like AMD, DR, PVR, glaucoma, and cataract.

Many endogenous causes of enhanced OS have been discovered, including phagocytosis of photoreceptor cells with defective outer segments, liposomes, and over ROS generation (Yang *et al.*, 2020). The phagocytosis and photooxidative stress of RPECs are responsible for the rapid formation of ROS (Nita and Grzybowski, 2016), (Trakkides *et al.*, 2019). There is enough evidence that suggests the link between OS and RPECs dysfunctions. However, it is very challenging to distinguish specific pathology in retinal tissue (Volobоueva *et al.*, 2005). The compromised or senescent RPECs were observed during different

conditions such as aging (Mishima *et al.*, 1999), low oxygen condition (Honda *et al.*, 2002), and light-induced stress (Ung *et al.*, 2017). Out of several ROS, hydrogen peroxide showed its damaging effects in RPECs. Due to the high metabolites activities, location, functions of RPECs, the presence of concentrations of hydrogen peroxide widely differs in ocular tissues (Yang *et al.*, 2006),(Spector *et al.*, 1998),(Yu *et al.*, 2009),(Huang *et al.*, 2014),(Zhao *et al.*, 2019). Many PVR patients found an increased concentration of H2O2 in the vitreous humor (Spector *et al.*, 1998). RPECs, where show slowly accumulated damage by OS (Wang *et al.*, 2013) but the reason behind the oculopathies and recorded data is still unavailable. By understanding the molecular mechanisms, it can be within our reach to treat many common but vision-threatening eye disorders (Ung *et al.*, 2017).

1.4.2 Oxidative stress and retinopathies

The accumulated damage of OS to vital macromolecules is also one of the factors in age-associated diseases (Inumaru *et al.*, 2009), (Yu *et al.*, 2009). Especially the retina is highly prone to OS-induced injury because of its higher oxygen tension, continuous exposure to light, and presence of high polyunsaturated fatty acids (PUFAs) (Jain *et al.*, 2013). It has been observed that OS is strongly associated with many ocular diseases like AMD and DR (Plafker *et al.*, 2012), (Yu *et al.*, 2009), (Khandhadia *et al.*, 2014). So, the RPECs are higher prone to OS (Huang *et al.*, 2014),(Zhao *et al.*, 2019) and result in various pathological conditions like age-related macular degeneration (AMD), diabetic retinopathy (DR), proliferative vitreoretinopathy (PVR) (Taylor *et al.*, 1992), (Rosen *et al.*, 2012).

1.4.3 Oxidative stress and diabetic retinopathy

The prolonged high glucose condition leads to retinopathy called diabetic retinopathy (DR), where abnormal vascularity is found which results in loss of normal vision (Tang and Kern, 2011) (Ung *et al.*, 2017). DR affects more than 280 million people worldwide (Yau *et al.*, 2012) which becomes the reason for vision loss in working-age individuals in developing countries (Grassi *et al.*, 2012), (Ung *et al.*, 2017). The DR is classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (Tang and Kern, 2011), (Ung *et al.*, 2017). The relationship between OS and DR is now well-established (Cui *et al.*, 2006), (Ung *et al.*, 2017). DR, ROS, and high glucose levels are all interlinked because high glucose levels are associated with the generation of ROS (Mullarkey *et al.*, 1990), (Li *et al.*, 2012), (Mateos, 2015) . The RPECs is the primary concern in PVR (Umazume *et al.*, 2014) as the RPECs are highly prone to epithelial-mesenchymal transition (EMT) (Tosi *et al.*, 2014). EMT is the transition of epithelial cells into mesenchymal cells under a disturbed microenvironment (Kalluri, 2009). Recently it has been observed that OS become the primary cause of initiation of EMT in RPECs (Inumaru *et al.*, 2009), (Tosi *et al.*, 2014). Fibrosis of retinal tissue including RPECs becomes the cause of PVR, PDR, and macula associated retinopathies (Yang *et al.*, 2020).

1.4.4 Oxidative stress and age-related macular degeneration

Age-related macular degeneration (AMD) becomes the major reason behind the loss of normal vision in aged individuals. It is generally defined as the loss of RPECs specifically in the macular region (Pascolini *et al.*, 2004), (Zhang *et al.*, 2016), (Ni *et al.*, 2019). The macular region is the part of the retina where the highest number of photoreceptors are located (Ung *et al.*, 2017). AMD is considered multifactorial retinopathy as it is caused by several factors such as genetic background, abnormal physiological inflammation, and OS (Zhang *et al.*, 2016). Choroidal neovascularization (CNV) and geographic atrophy (GA) are characteristics of wet-AMD and dry-AMD respectively (Jager *et al.*, 2008), (Zhang *et al.*, 2016). The GA refers to abnormal choriocapillaris, disrupted photoreceptors, and RPECs (Zhang *et al.*, 2016),(Kamoshita *et al.*, 2016). The CNV is referred to as the new blood vessels formation with scarring tissue around the RPECs (Beatty *et al.*, 2000), (Bird *et al.*, 1995). The dry-AMD and wet-AMD can be differentiated by eye examination. The dry-AMD (also known as early- AMD) showed soft drusen and depigmented RPECs. The wet-AMD (late-AMD) showed low-pigmented or depigmented or absence of RPECs in the macular region (Bird *et al.*, 1995), (Beatty *et al.*, 2000). It has been observed that OS is the main pathological factor in AMD (Beatty *et al.*, 2000). Besides OS some other external factors are also involved such as smoking, daylight exposure, and low diet-antioxidants to contribute to AMD progression (Seddon *et al.*, 1994),(Samiec *et al.*, 1998), (Smith *et al.*, 2001) (see figure 3). The OS affects the RPECs in many aspects such as loss of blood-retinal barrier, the disintegration of tight junctions, and the disrupted tight junctions is the notable character of AMD

(Rizzolo, 2014). Finding the exact pathogenesis of AMD is challenging as the role of OS is slow and progressive (Zhang *et al.*, 2016). Many *in vitro* studies suggested OS-induced injuries showed similarity with AMD in retinal tissue (Del Priore *et al.*, 2002),(Cano *et al.*, 2014), (Angulo Daniela, 2015),(Ni *et al.*, 2019). Recently the apocynin was observed as neuroprotective by blocking ROS generation (Ung *et al.*, 2017). The AREDS suggested lutein as a beneficial supplement for vision improvement (Kamoshita *et al.*, 2016). As mentioned earlier antioxidants play a beneficial role to fight against ROS-mediated injury. Its level gives clues about the health of any living system so, the levels of SOD, CAT GSH-Px, GR in RPECs are reasonable to understand the severity of the disease.

1.5 Superoxide dismutase

Superoxide dismutase (SOD) is an antioxidant enzyme that has the main function is to converting superoxide radicals into water and molecular oxygen. Especially in the retina the RPECs and photoreceptors are protected from photooxidative damage, where along with SOD other antioxidants such as GSH-Px, CAT contributes to their function (Cohen *et al.*, 1994), (Plestina-Borjan *et al.*, 2015). There are three mammalian isoforms of SODs that are known which are encoded by gene SOD1, SOD2, and SOD3 (Ung *et al.*, 2017). The SOD1, a copper-zinc superoxide dismutase (Cu/ZnSOD) primarily found in the cytosolic part of the cell, the SOD2, a manganese superoxide dismutase (Mn-SOD) which is primarily localized in mitochondria, and the SOD3, an extracellular superoxide dismutase (EC-SOD) which mainly found in the extracellular part of the cellular system (Helmut Sies *et al.*, 2017). In normal physiology SOD1 (Cu/ZnSOD) molecule traveled into the nucleus and there it activates several related beneficial genes that show protective function against ROS (Beatty *et al.*, 2000), (Ung *et al.*, 2017). The importance of enzyme SODs can be appreciated by understanding their normal homeostasis. The lack of the SOD gene and its related proteins showed various detrimental effects which may be due to the modification of macromolecules such as protein, lipids, and DNA (Behndig, 2008), (Kliment *et al.*, 2009), (Lee *et al.*, 2013), (Schieber and Chandel, 2014). Moron and colleagues suspect the damaging effects due to decreased SOD activity (Moron *et al.*, 1979). Furthermore, protein or enzyme denaturation by hydrogen peroxide-induced OS may result in a decrease in SOD activity as observed in diabetes mellitus (Sajeeth *et al.*, 2011). The reduction in SOD activity was observed by many researchers under different conditions. The acrolein-treated ARPE-19 cells showed reduced SOD activity under stress compared to control (Liu *et al.*, 2007), (Jia *et al.*, 2007). The peripheral RPECs showed decreased SOD activity (Qin and Gerard A Rodrigues, 2008). The decrease SOD level found in serum of AMD Chinese population (Jia *et al.*, 2011)(Shen *et al.*, 2012), (Venza *et al.*, 2012). ROS-generation and decreased SOD activity are also found in RPECs (Li *et al.*, 2012), (Mateos, 2015). The increased SOD immunoreactivity and decreased activity were found associated with age in peripheral RPECs (Qin and Gerard A Rodrigues, 2008). Venza and coworkers found decreased SOD activity in blood plasm and RBC of AMD patients (Venza *et al.*, 2012). Lack of SOD gene linked with detrimental effects on macromolecules (Schieber and Chandel, 2014). However, the upregulated SOD1/2 gene expression was found in OS-damaged RPECs (Lu *et al.*, 2009). *In vitro* study on ARPE-19, the RPECs cell line showed the lutein as the regulator of SOD activity (Kamoshita *et al.*, 2016). In contrast to the above results inconsistencies in data of SOD activity are observed in retinopathies. There was no correlation observed between AMD and SOD activity (Delcourt *et al.*, 1999). In addition to that unaltered SOD activity was found in people of various age groups from children to aged individuals at different locations of the retina (De La Paz *et al.*, 1996). SOD1 immunoreactivity was also checked in normal and with choroidal neovascular membranes (CNVM) eyes by Frank and co-workers (Frank *et al.*, 1999). Further in RPECs, the change in SOD activity was not associated with age (Liles *et al.*, 1991). So, based on the above-mentioned outcomes it appeared that the antioxidant, SOD only acts as a local antioxidant (Beatty *et al.*, 2000).

1.6 Catalase

Usually, catalase (CAT) activity is observed in the specialized cellular compartment, the peroxisome. It is largely dependent on iron (Fe^{+}) for its normal functioning (Chance *et al.*, 1979),(Halliwell, 1991). Its main function is to produce harmless substances such as water and molecular oxygen from hydrogen peroxide, a product of various metabolic processes (Chance *et al.*, 1979), (Liles *et al.*, 1991),(Frank *et al.*, 1999),(Beatty *et al.*, 2000), (Weydert and Cullen, 2010). More CAT means less cytotoxicity (Gille and Joenje, 1992). Interestingly it is also found in human photoreceptors and RPECs (De La Paz *et al.*, 1996), (Liles *et al.*, 1991), (Frank *et al.*, 1999). The stress-

stimulating compounds are associated with the expression of CAT (Miceli *et al.*, 1994) ,(Tate, 1995). CAT showed a protective role in RPECs and other surrounding tissue (Haque *et al.*, 2012). The increased CAT activity was observed during the phagocytosis in RPECs, probably in response to increased hydrogen peroxide concentration (Tate, 1995). Furthermore, the CAT and metallothionein were found overexpressed under OS conditions (Beatty *et al.*, 2000). The CAT level was found higher in normal RPECs but it was found highly decreased in AMD patients' eyes (Liles *et al.*, 1991). So, the CAT activity decreases as AMD progresses (Herrmann *et al.*, 1984),(Liles *et al.*, 1991). In RBC also decreased CAT activity was observed in AMD patients to control (Ulańczyk *et al.*, 2020). Low CAT immunoreactivity was observed in AMD conditions (Frank *et al.*, 1999). *Cynomolgus* monkeys also showed decreased CAT activity compared to the control (De La Paz *et al.*, 1996). Haque and co-workers found the link between ROS and CAT expression at both transcript and protein levels (Haque *et al.*, 2012). Recently many studies showed the CAT as a protective agent against RPECs and photoreceptors (Rex *et al.*, 2004). From various studies, it can observe that there is a correlation between CAT activity and AMD. Additionally, it also seems that CAT very a vital component as an antioxidant (Beatty *et al.*, 2000). So, it is observed that a decrease in CAT activity is prone to harmful effects from ROS (Moron *et al.*, 1979). Interestingly in vivo study suggested the use of ROS-scavengers to maintain CAT activity (Sajeeth *et al.*, 2011). However, some researchers showed no change in CAT activity such as a non-significant change in CAT activity when cells were exposed to a lower concentration of hydrogen peroxide which may alter at a higher concentration of hydrogen peroxide (Miyamura *et al.*, 2004), (Angulo Daniela, 2015). Further also no changes in CAT activity were reported (Novack and Stefánsson, 1990), (Miceli *et al.*, 1994). Miyamura and coworkers in the study of RPECs showed that CAT activity or mRNA expressions are not associated with aging (Miyamura *et al.*, 2004). In support of this, there are no oculopathies associated with a lack of CAT genes (Beatty *et al.*, 2000). Frank and colleagues showed an inverse relationship between CAT activity and age but were not associated with and without AMD (Frank *et al.*, 1999). From all results, it seems that the role of CAT is very complex in nature for maintaining OS and protection of retinal tissue such as RPECs (Lee *et al.*, 2012).

1.7 Glutathione peroxidase

Glutathione peroxidase (GSH-Px) is the predominant family of selenoenzyme antioxidants that converts lipid hydroperoxide as well as hydrogen peroxide into less harmful products. It consumes electron donor glutathione (GSSG/GSH) during the chemical reaction (Gille and Joenje, 1992), (Tabatabaie and Floyd, 1994), (Beatty *et al.*, 2000),(Lubos *et al.*, 2011), (Ung *et al.*, 2017). GSH-Px showed a protective function on the genome and ultimately contributes to preventing cell death (Tokarz *et al.*, 2013). There are five known isoenzymes of GSH-Px (De Haan *et al.*, 1998). Among them, the GSH-Px-1 is a cytosolic selenoprotein that was first described as a regulator of oxidative injury in RBCs. Especially the plasma-GSH-Px is a non-cellular form of the enzyme (Maddipati and Marnett, 1987) which is predominantly found in almost all ocular tissues (Chu *et al.*, 1992). It is strongly believed that plasma-GSH-Px activity is associated with AMD and oculopathies (Beatty *et al.*, 2000). Decreased GSH-Px activity was observed due to alteration in the structure and content of protein (Meister, 1984). In diabetic rats, it was observed that the degradation of protein is prevented by the presence of GSH-Px (Sajeeth *et al.*, 2011). Overexpressed GSH-Px mitigates ROS-mediated injury like apoptosis (Kelner *et al.*, 1995),(Kayanoki *et al.*, 1996),(Weydert and Cullen, 2010). The overexpression of GSH-Px4 helped in protection from SOD1/2-induced oxidative injury (Tokarz *et al.*, 2013). More interestingly overexpression of it helped in mitigating the injury from OS (Kelner *et al.*, 1995), (Valko *et al.*, 2006), (Weydert and Cullen, 2010) and it also helped in downregulating apoptosis, especially induced by hydrogen peroxide (Kayanoki *et al.*, 1996). A higher level of GSH-Px activity was observed in AMD patients (Nicolas *et al.*, 1996), (Delcourt *et al.*, 1999). The POLA study of AMD on 2,584 individuals showed correlations with increased plasma-GSH-Px and helped to delay late-AMD occurrence (Delcourt *et al.*, 1999). Ohira and coworkers revealed the upregulation of GSH-Px in an immunohistochemistry study of mice where OS was induced by fluorescent light (Ohira *et al.*, 2003). The *in vitro* study revealed the upregulation of GSH-Px4 or GSH-Px1 in response to OS in RBCs. Additionally, the upregulated GSH-Px4 or GSH-Px1 help to deaccelerate the carbonylation of protein especially resulting from the treatment of stress-inducing substances such as H2O2 and paraquat (Ueta *et al.*, 2012). A study in early-AMD *Cynomolgus* monkeys showed the upregulated GSH-Px activity (Nicolas *et al.*, 1996). The increase and decrease in

GSH-Px activity are associated with AMD (Plestina-Borjan *et al.*, 2015) ,(Mrowicka *et al.*, 2017) , (Ulańczyk *et al.*, 2020). So, it has become a good indicator of AMD in some severe oculopathy patients (Maddipati and Marnett, 1987), (Beatty *et al.*, 2000).

1.8 Glutathione reductase and reduced glutathione (GSH)

Glutathione reductase (GR) is very essential for the regeneration of glutathione (GSSG/GSH). It does not directly act as an antioxidant but very essential for the normal functioning of other crucial antioxidants. The tripeptide glutathione is found in the mammalian neurosensory retina, which has a major role in neutralizing ROS by oxidation-reduction reactions. The bovine retina where showed protective functions independent of retinol to PUFAs of the neurosensory retina (Keys and Zimmerman, 1999). Some studies showed that the low level of plasma-GR is linked with retinopathy like AMD (Beatty *et al.*, 2000),(Cohen *et al.*, 1994). But still, there is very little correlation between GR-activity and the severity of retinopathies (De La Paz *et al.*, 1996).

Reduced glutathione, a sulfhydryl containing amino acid chain (Angulo Daniela, 2015), plays a very important role in scavenging ROS and conversion of hydroperoxides and hydrogen peroxide into less harmful molecules in the presence of GSH-Px by utilization of thiol group and hence protects crucial biological molecules (Sajeeth *et al.*, 2011), (Tokarz *et al.*, 2013) which indirectly helps in reduction of lipid peroxidation (LPO) (Chance *et al.*, 1979). In diabetes, a positive correlation between OS and glutathione content was observed (Guruvayoorappan, 2008). One *in vitro* study suggested its level decreases as the concentration of hydrogen peroxide increases in cells and oxidation of it leads to major cellular damage (Angulo Daniela, 2015). As the conversion of GSH to GSSG is cyclical changes, the ratio of GSH to GSSG is an indicator of stress level, and the reduced GSH also acts as cofactors for GSH-Px and GST (glutathione S-transferases) (Tabatabaie and Floyd, 1994). The cellular functions behave differently at different concentrations of reduced glutathione. As all the vital cellular activities were sustained at higher concentrations (more than 1 mM GSH) while, the cells were prone to OS-injury at lower concentrations (less than 0.1 mM GSH) and the least concentration (0.03 mM GSH) the cell leads to death (Hatem *et al.*, 2014) (Angulo Daniela, 2015). So, it seems that a minimum concentration of GSH-Px is necessary to protect the cellular and nuclear activities from OS (Hatem *et al.*, 2014). Under a low concentration of glutathione, the DNA stability is highly affected (Hatem *et al.*, 2014), (Angulo Daniela, 2015). As the GSH-Px is associated with maintaining the ratio of GSSG to GSH (Tabatabaie and Floyd, 1994), the GSH depletion may contribute to OS (Tokarz *et al.*, 2013) as well retinopathy like AMD (Cohen *et al.*, 1994). Decreased reduced-GSH and increased oxidized-GSSG were observed in aged individuals (Samiec *et al.*, 1998). A low level of GSH was observed in AMD patients (Cohen *et al.*, 1994) which may lead to apoptosis of RPECs (Glotin *et al.*, 2006). Some other studies also found a link of decreased plasm-GSH with age (Lang *et al.*, 1992),(Lang *et al.*, 1992),(Kretzschmar and Müller, 1993),(Samiec *et al.*, 1998). Furthermore, *in vitro* study on ARPE-19 cells under tert-butylhydroperoxide (t-BHP)-induced stress, the GSH level was found to decrease, additionally apoptotic cell death was also observed in the response of ROS (Glotin *et al.*, 2006). Some other studies also showed that decreased plasm-GSH with age and RPECs were found susceptible to OS (Samiec *et al.*, 1998),(Volobоueva *et al.*, 2005). Interestingly the increased GSH level was seen in diabetic patients upon the administration of antioxidant homologs (Sajeeth *et al.*, 2011).

1.9 Lipid peroxidation

The damaging lipid peroxidation (LPO) chain once started destroys many macromolecules as it is observed that hydroxyl radicals are involved in LPO and DNA damage (Gille and Joenje, 1992), (Beatty *et al.*, 2000). So, OS is directly correlated with LPO and hence disintegrates the membrane of the cell and affects the membrane permeability (Antunes and Cadenas, 2000), (Makino *et al.*, 2008), (Gülden *et al.*, 2010), (Panieri *et al.*, 2013). PUFAs like docosahexaenoic acid (DHA) are found in high amounts in photoreceptors and RPECs (Fliesler and Anderson, 1983) which are the prime target of LPO (Mukherjee *et al.*, 2004). In RPECs, the free lipid-radical auto-oxidation, the process of formation of lipid-peroxyl and lipid-hydroxide radical, which are highly expected due to the availability of PUFAs which possess conjugated double bonds which become a readily available source of the hydrogen atom which contain one electron. Hence it starts a chain of cytotoxic cascades and consumes valuable PUFAs and degradation of it resulted in a product like malondialdehyde (MDA), a marker of lipid

peroxidation (Halliwell, 1991), (Beatty *et al.*, 2000). Due to phagocytosis, which is the primary function of RPECs, the generation of hydrogen peroxide increases and thus resulting in LPO (Ramachandran *et al.*, 1991), (Miceli *et al.*, 1994), (Taguchi *et al.*, 1996) (Spector *et al.*, 1998), (Kim *et al.*, 2003), (Yang *et al.*, 2006), (Yu *et al.*, 2009). In RPECs a higher LPO was observed when CAT was inhibited (Miceli *et al.*, 1994). Additionally, several other studies suggested that the retina is susceptible to LPO (Tate *et al.*, 1999), (Yu *et al.*, 2009),(Ung *et al.*, 2017). Furthermore, the LPO in the human retina is age-dependent (Beatty *et al.*, 2000). An interesting link was found between the GSH-Px and LPO in rats (Sajeeth *et al.*, 2011) and more interestingly LPO is considered the marker of diabetes (Guruvayoorappan, 2008).

2. DISCUSSION

The study of antioxidants in peripheral blood suggested GSH-Px, R-GSSG, and GST level in RBCs and SOD, CAT, GSH-Px, and reduced-GSH levels in platelets found increased in AMD patients (Ulańczyk *et al.*, 2020). Currently, there is no permanent therapy for AMD (Ni *et al.*, 2019),(Wolf, 2008). Many studies suggested that ROS-mediated apoptosis can be altered by using antioxidants (Yu *et al.*, 2009). It has been observed that the supplementation of antioxidants and zinc deaccelerates the progression of retinopathy (Voloboueva *et al.*, 2005), (Yu *et al.*, 2009). Further, the National Health and Nutrition Examination Survey (NHANES) also suggested a positive relation between intakes of antioxidants containing food and AMD suppression (Goldberg *et al.*, 1988). The decrease in antioxidants results in abnormal neovascularisation as observed in AMD (Ung *et al.*, 2017),(Zhao *et al.*, 2019). Interestingly the administration of phytochemicals helped to maintain cellular SOD status (Sajeeth *et al.*, 2011). More interestingly the data from recent research reveals that the antioxidant homologs proved useful to re-establish the antioxidant status (Liu *et al.*, 2016), (Ni *et al.*, 2019). Recently the link between ROS and EMT (epithelial-mesenchymal transition) (Yang *et al.*, 2020). The evidence for the significance of OS in a wide range of ocular illnesses begs the question of whether therapeutic approaches may be developed to either reduce the harmful effects of high ROS concentrations or supplement our natural defense systems against them. Although experimental evidence suggests that oxidative damage occurs in the retina and RPECs, the relationship between these processes and the onset of retinopathy remains uncertain. In summary, the current evidence on the association between antioxidants level and retinopathies is inconclusive, yet antioxidants appear to play a critical role in resisting retinopathies.

3. CONCLUSION

Oxidative stress damages RPECs, resulting in a broad range of retinopathies. Because of its high oxygen consumption, high amount of polyunsaturated fatty acids, and exposure to visible light, the retina is particularly vulnerable to OS. Antioxidants counteract the effects of ROS and hence aid in the prevention of retinopathies. Overall understanding of OS and retinal pigment epithelium suggest that an altered balance of antioxidants and stress leads to retinopathy such as AMD, DR, and PVR.

Abbreviations used

AMD	: Age-related macular degeneration
ARPE-19	: A retinal pigment epithelial cell line
BRB	: Blood retinal barriers
CAT	: Catalase
DR	: Diabetic retinopathy
GSH-Px	: Glutathione peroxidase
GR	: Glutathione reductase
H2O2	: Hydrogen peroxide
LPO	: Lipid peroxidation
NHANES	: National Health and Nutrition Examination Survey
PVR	: Proliferative vitreoretinopathy
SOD	: Superoxide dismutase

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