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SCIELL

THE TOXIC EFFECT OF HYPERGLYCAEMIA IN THE PATHOGENESIS OF SELECTED CHRONIC COMPLICATIONS OF *DIABETES MELLITUS*: A MINI-REVIEW

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ABSTRACT

Diabetes mellitus is a group of metabolic diseases that, due to the long-term pathological effect of hyperglycaemia on tissues, lead to the development of typical chronic organ complications. Chronic hyperglycaemia leads to increased activity of the polyol pathway with subsequent accumulation of sorbitol and fructose, increased formation and accumulation of end products of advanced glycation, alteration of protein kinase C activity, excessive formation of reactive oxygen species and associated high level of oxidative stress. One of the most feared complications of *diabetes mellitus* is vision impairment and blindness. In this review, we address the most important metabolic pathways leading to the development of diabetic retinopathy and diabetic cataract, the ocular complications of diabetes with the greatest risk of vision loss.

Key words: diabetes; hyperglycaemia; cataract; diabetic retinopathy

INTRODUCTION

Diabetes mellitus (DM) is defined as a group of metabolic diseases that arise as a result of disorder either of insulin secretion, or its action in tissues, or a combination of both. The consequence of the long-term pathological effect of hyperglycaemia on tissues is the development of typical chronic organ complications. These are traditionally divided into microangiopathies with damage to small vessels (retinopathy, nephropathy and neuropathy) and macroangiopathies with atherosclerotic changes primarily in large arteries (coronary, brain and lower limb vessels) (Kiňová *et al*., 2013; Češka *et al*., 2015; Sosna *et al*., 2016). One of the most feared complications of *diabetes mellitus* is vision impairment and blindness. The eye complications of diabetes with the greatest risk of vision loss include diabetic retinopathy and diabetic cataracts. In recent decades, there has been a growing effort to understand and describe mechanisms leading to the development of chronic complications of diabetes. This trend is a promise for targeted treatment, based on influencing individual participating metabolic pathways. The common denominator is a chronic hyperglycaemia, which leads to increased activity of the polyol pathway with subsequent accumulation of sorbitol and fructose. Moreover, chronic hyperglycaemia affects the activity of protein kinase C, causing increased formation and subsequent accumulation of advanced glycation end products (AGEs), and leads to an increased level of oxidative stress due to excessive formation of reactive oxygen species (ROS) (Figure 1). The pathophysiology of the development

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of diabetic complications is a complex process, where individual mechanisms do not act in isolation but always in mutual, often very complex interactions (Karasova *et al*., 2014; Wu *et al*., 2014; Soltesova-Prnová *et al*., 2015; Kimaková *et al*., 2017; Prnová, 2019; Wong *et al*., 2018; Heruye, 2020).

CATARACT

Even in the 21st century, cataracts are the main cause of blindness in the world, affecting around 94 million people (Kuchynka *et al*., 2016; WHO, 2019; Heruye, 2020). Only the inhabitants of the most developed countries of the world have unrestricted access to surgical treatment; for the majority of people on earth it remains inaccessible. These facts imply an effort to find a preparation that could prevent or slow down the progression of the disease without the need for surgery, which would mean a huge benefit, especially for regions with limited possibilities of microsurgical treatment (Doganay *et al*., 2006; Shetty *et al*., 2010; Mathew *et al*., 2012; Dubey *et al*., 2016; Braakhuis *et al*., 2019; Lim *et al*., 2020; Xu *et al*., 2020). The results of experimental works focused on the research of the anticataractogenic effect of various substances show that substances with antioxidant potential are of fundamental importance. Experiments are usually performed on animal models (most commonly Wistar rats, mice, rabbits, dogs etc.), in which cataract development is induced by oxidative stress, metabolic disease, UV radiation or steroid administration (Yamakoshi *et al*., 2002; Dukuran *et al*., 2006; Heruye, 2020) The most frequently investigated substances include the antioxidants: vitamin C, vitamin E, glutathione, carotenoids, the flavonoid quercetin and the polyphenol resveratrol (Singh *et al*., 2019, Lim *et al*., 2020; Hrnková *et al*., 2021a). The anticataractogenic effect is very likely to inhibit the oxidation of lipids, proteins, nucleic acids and peroxide formation (Doganay *et al*., 2006; Shetty *et al*., 2010; Dubey *et al*., 2016). In our experiments, we use the Zucker diabetic fatty (ZDF) rats as an animal model for the research of the diabetic complications, including the ocular manifestations of the diseases (Capcarova *et al*. 2018; Hrnkova, 2021b). The main causes of the cataract development are age, genetic predisposition, congenital mutations of lens proteins, physical environmental influences and overproduction of sugar alcohols due to metabolic diseases, especially *diabetes mellitus* (Kanski, 2008; Obrosova *et al*, 2010; Kuchynka *et al*., 2016; Tan *et al*., 2019; Heruye, 2020). In the pathogenesis of diabetic cataracts, activation of the polyol pathway with the accumulation of sorbitol and pathological accumulation of advanced glycation end products (AGEs) are essential (Obrosova *et al*., 2010; Drinkwater *et al*., 2019; Salmon, 2020). The final result of all these processes is excessive oxidative stress, which leads to exhaustion or failure of the antioxidant system of the lens with subsequent development of cataracts; the lens loses its transparency, vision deteriorates and, without treatment, falls to the level of blindness (Dukuran *et al*., 2006; Kuchynka *et al*., 2016; Heruye, 2020).

DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is the most common microvascular complication of *diabetes mellitus* and the main cause of blindness in the adult population in developed countries. The prevalence of DR was around 27 % in 2019, which means that of the 463 million diabetics, approximately 125 million had some form of diabetic retinopathy (Matos, 2020). Risk factors for the development of diabetic retinopathy include the duration of the underlying disease, its lack of compensation, associated diseases such as arterial hypertension and dyslipidaemia (Kuchynka, 2016; Matos, 2020). The basic pathomechanism of the development of diabetic retinopathy is the pathological effect of chronic hyperglycaemia on the endothelial vessels. At the cellular level, it is a chronic inflammation that leads to an increase in oxidative stress with subsequent damage to the microcirculation of the retina. The retinal pigment epithelium (RPE) is of fundamental importance, where excessive accumulation of sorbitol occurs, a high concentration of diacylglycerol, activated enzyme protein kinase C (PKC) and also products of late glycation of proteins (AGEs) has been proven in the RPE cells. As a result of damage to the RPE, the external and internal hematoretinal barrier collapses, this facilitates the penetration of proliferation factors into the vitreous (e.g. vascular endothelial growth factor, VEGF). This increases the proliferative

potential of the eye, which leads to the development and progression of diabetic retinopathy into severe forms. Such pathological changes can result in irreversible vision damage (Lee *et al*., 2010; Sosna *et al*., 2016; Kuchynka *et al*., 2016; Studnička, 2018; Salmon, 2020; Matos, 2020).

POLYOL PATHWAY

The polyol pathway takes place in two phases. In the first one, glucose is metabolized to sorbitol in the presence of the enzyme aldose reductase (ALR2) and the cofactor NADPH (nicotinamide adenine dinucleotide phosphate), which is converted to NADP+ (Figure 1). Since sorbitol is unable to diffuse through membranes, it accumulates in cells, binds water and causes an electrolyte imbalance and development of osmotic oxidative stress. Due to the depletion of antioxidant mechanisms, cataracts develop together with the damage to peripheral nerves and disruption of endothelial cells of the capillary bed (Obrosova *et al*., 2010; Prnová, 2019; Kiziltoprak *et al*., 2019; Salmon, 2020). In the next phase of the polyol pathway, sorbitol is metabolized to fructose by the action of the enzyme sorbitol dehydrogenase in the presence of the cofactor NAD+ (nicotinamide adenine dinucleotide), which is converted to NADH. NADPH is consumed by the polyol pathway, which leads to a decrease in the level of glutathione and, thus, to a decrease in the body defence against oxidative stress. NAD+ is regenerated by oxidation, which produces ROS. At the same time, due to the increasing ratio of NADH:NAD+ the latter inhibits the activity of the enzyme glyceraldehyde-3-phosphate dehydrogenase, which leads to an increase in the level of triose phosphates. These induce increased formation of methylglyoxal (a precursor of AGEs) and diacylglycerol (DAG), which activates PKC (Figure 1). Thus, the polyol pathway also participates in increasing the concentration of late glycation products. Depletion of NAD+ leads to the deactivation of the Sirt1 protein, which affects the production of insulin in the pancreatic β-cells and, through adipokines, affects the development of insulin resistance in tissues (Prnová, 2019). The result is an excessive oxidative stress leading to the development of chronic tissue damage, including cataracts and diabetic retinopathy (Reddy *et al*., 2012; Kador *et al*., 2012; Kotas *et al*., 2012; Karasova *et al*., 2014; Soltesova-Prnova *et al*., 2015; Prnová, 2019; Yan, 2018; Ohno *et al*., 2019). Several aldose reductase inhibitors (mostly bioflavonoid derivatives) have been studied in animal models with very promising results, but this positive effect has not yet been confirmed in clinical studies (Kotas *et al*., 2012; Milackova *et al*., 2014; Karasova *et al*., 2014; Soltesova-Prnova *et al*., 2015; Prnová, 2019).

HEXOSAMINE PATHWAY, PROTEIN KINASE C

In the environment of hyperglycaemia, glycolysis occurs, intermediate products such as glucose-6- phosphate (G-6-P) and fructose-6-phosphate (F-6-P) are formed, which enter the hexosamine pathway, where uridine-5-diphosphate- N-acetyl-glucosamine (GlcNac) is formed (Figure 1). This is able to bind to several transcription factors, such as Sp-1, leading to inflammation and tissue damage with passive glucose transport. Increased glycolysis also leads to the accumulation of DAG, which activates the PKC enzyme (Figure 1). PKC is closely related to many metabolic disorders associated with insulin resistance and changes in the gene expression for VEGF. The result is vasoconstriction, hypoxia and the development of diabetic retinopathy, peripheral neuropathy and nephropathy (Kotas *et al*., 2012; Prnová, 2019).

NON-ENZYMATIC GLYCATION OF PROTEINS

Glucose binds non-enzymatically to the amino acids of proteins and early glycation products (Schiff base, Amadori products) are formed, which are then converted into late glycation products (AGEs) during the Maillard reaction (Figure 1). These bind to essential proteins and irreversibly change their function. They are able to activate many receptors, thereby affecting several signalling processes in cells leading to tissue damage. The connection to the so-called RAGE receptor on macrophages, which then activates kappa B nuclear factor (Nf κB), leading to increased production of endothelin, tissue factor, thrombomodulin and VCAM1 adhesion molecules, is highly important. The result is a vasoconstriction, procoagulant state and chronic inflammation in the

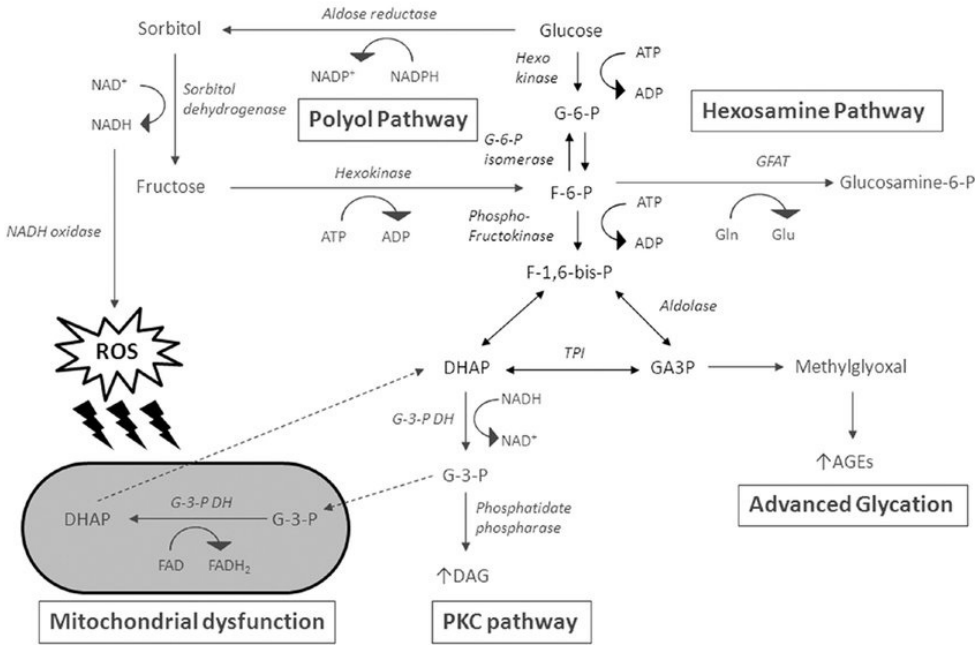

Figure 1. The most important metabolic pathways leading to the development of diabetic complications (Tang *et al*., 2012)

affected tissue (Kotas *et al*., 2012; Prnová, 2019). The excessive accumulation of AGEs has a toxic effect on pericytes and the endothelium of retinal vessels, which leads to irreversible damage to the microcirculation and the development of DR (Sosna *et al*., 2016). In experimental conditions, aminoguanidine proved to be a promising AGE inhibitor, but several of its undesirable effects were shown in clinical studies (Feldman *et al*., 2017; Prnová, 2019).

CONCLUSION

Diabetes mellitus is considered a pandemic of the 21st century. As the number of diabetics increases, so does the incidence of serious complications of DM, which has significant health, social and economic consequences for society. Understanding the mechanisms involved in the pathogenesis of chronic complications of diabetes is of fundamental importance for targeted treatment, based on the influence of individual participating metabolic pathways.

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AUTHOR CONTRIBUTIONS

Conceptualization: Capcarová, M., Hrnková, J.
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Project administration: Capcarová, M.

All authors have read and agreed to the published version of the manuscript.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Braakhuis, A. J., Donaldson, C. I. & Lim, J. C. (2019). Nutritional Strategies to Prevent Lens Cataract: Current Status and Future Strategies. *Nutrients*, 11(5), 1186. https://doi.org/ 10.3390/nu11051186

Capcarova, M., Soltesova Prnova, M., Svik, K. & Schneidgenova, M. (2018). Rodent animal model for research in diabetes: a mini-review. S*lovak Journal of Animal Science*, 51(3), 138−145.

Češka, R., Štulc, T., Tesař, V. & Lukáš, M. (2015) *Interna, svazek 1*. Triton Praha, 332 s., ISBN 978-80-7387-895

Doganay, S., Borazan, M. & Iraz, M. (2006). The effect of resveratrol in experimental cataract model formed by sodium selenite. *Current Eye Research*, 31(2), 147−153. https://doi.org/10.1080/02713680500514685

Drinkwater, J. I., Davis, W. A. & Davis, T. M. E. (2019). A systemic review of risk factors for cataract in type 2 diabetes. *Diabetes Metabolism Research and Reviews*, 35(1), e3037. https://doi.org/10.1002/dmrr.3073

Dubey, S., Deep, P. & Singh, A. K. (2016). Phytochemical characterization and evaluation of anticataract potential of seabuckthorn leaf extract. *Veterinary Ophthalmology*, 19(2), 144-148 https://doi.org/ 10.1111/vop.12271

Dukuran, A. H., Everekliogl u, C. & Hurmeric, V. (2006). Ingestion of IH636 grape seed proanthocyanidin extract to prevent selenite- induced oxidative stress in experimental cataract. *Journal of Cataract and Refractive Surgery*, 32(6), 1041−1045. https://doi.org/ 10.1016/j.jcrs.2006.02.041

Feldman, E. L., Bennett, D. L. & Nave, K. A. (2017). New horizons in diabetic neuropathy: Mechanism, Bioenergetics, and Pain. *Neuron*, 93(6), 1296−1313. https://doi.org/ 10.1016/j.neuron.2017.02.005.

Heruye, S. H., Nkenyi, L. N. M., Singh, N. U. & Yalzadeh D. (2020). Current Trends in the Pharmacotherapy of Cataracts. *Pharmaceuticals (Basel)*, 13(1), 15. https:// doi.org/ 10.3390/ph13010015

Hrnková, J., Dupák, R. & Capcarová, M. (2021a). Rakytník rešetliakový − potenciálny kandidát pre farmakologickú liečbu katarakty? *24. Košický morfologický deň*, zborník vedeckých prác, Univerzita veterinárskeho lekárstva a farmácie v Košiciach, s. 121−125. ISBN 978-80-8077-705-0

Hrnkova, J. (2021b). Effect of sea buckthorn extract on the development of cataracts in ZDF rats. *Scientific Conference of PhD. Students of FAFR, FBFS and FHLE SUA in Nitra*. Slovak University of Agriculture, p. 12. ISBN 978-80-552-2400-8

Kador, P. F., Wyman, M. & Oastes, P. J. (2016). Aldose reductase, ocular diabetic complications and the development of topical Kinostat. *Progress in Retinal and Eye Tesearch*, 54, 1−29. https://doi.org/10.1016/j. preteyeres.2016.04.006

Kanski, J. J. (2008). *Klinische Ophthalmologie*, Lehrbuch und Atlas. 6. Auflage, Elsevier, Munchen, p. 974. ISBN 978-3-437-23472-9

Karasova, M. J., Soltesova-Prnova, M. & Stefek, M. (2014). A novel zwitterionic inhibitor of aldose reductase interferes with polyol pathway in *ex vivo* and *in vivo* models of diabetic complications. *Pharmazie*, 69(10), 747−751.

Kiňová, S., Hulín, I., Čamborová, P., Ďuriš, I., Ferenčík, M., Maasová, D., Lukáč, Ľ., Štvrtinová, V. & Valášková, V. (2013). *Interná medicína*, Prolitera Bratislava, 1136 s. ISBN 978-80-970253-9-7

Kimaková, T. & Pavlík, V. (2017). *Antioxidanty a ich význam v prevencii chronických ochorení*. Vedecká monografia, UPJŠ v Košiciach, 154 s. ISBN 978-80-8152-512-4

Kiziltoprak, H., Tekin, K. & Inanc, M. (2019). Cataract in *diabetes mellitus*. *World Journal of Diabetes*, 10(3), 140−153. https://doi.org/10.4239/wjd. v10.i3.140

Kotas, R. & Ambler, Z. (2012). Patofyziologie diabetické neuropatie. *Neuroligie pro praxi*, 13(Suppl.E), 7−11.

Kuchynka, P., Autrata, R., Boguszaková, J., Diblík, P., Hlinomazová, Z., Kocur, I., Kuchynková, Z., Lichneová, I., Lišková, P., Maňáková, E., Novák, J., Pašta, J., Rezek, P., Řehořová, J., Říhová, E., Studený, P., Šach, J., Veith, M., Vlková, E., Borovanský, J., Brichová, M., Heissigerová, J., Hladíková, M., Konvička, J., Krásný, J., Krutílková, V., Matušková, V., Michalcová, L., Moravcová, D., Novák, P., Pešková, H., Rokyta, R., Sosna, T., Stejskal, D., Studnička, J., Svozílková, P., Šišková, A. & Vokrojová, M. (2016). Oční lékařství, 2. vyd., Grada Praha, 936 s. ISBN 978-80-271-9182-6

Lee, Ch., Gayton, E. L. & Beulens, J. W. (2010). Micronutrients and Diabetic Retinopathy: A systematic. Ophthalmology, 117(1), 71−78. https://doi.org/10.1016/j.ophtha.2009.06.040

Lim, J. C., Arredondo, M. C. & Braakhuis, A. J. (2020). Vitamin C and the Lens: New Insights into Delaying the Onset of Cataract. *Nutrients*, 12(10), 3142. https://doi.org/10.3390/nu12103142

Mathew, M. C., Ervin, A. M., Tao, J. & Davis, R. M. (2012). Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. The Cochrane Database of Systematic Reviews, 6(6), CD004567. https://doi.org/10.1002/146551858.CD004567.pub.2

Matos, A. L., Bruno, D. F., Ambrosio, A. F. & Santos P. F. (2020). The Benefits of Flavonoids in Diabetic retinopathy. *Nutrients*, 12(10), 3169. https://doi.org/10.3390/nu12103169

Milackova, I., Soltesova-Prnova, M. & Majekova, M. (2014). 2-chloro-1,4 naphtoquinone derivate of quercetin as an inhibitor of ladose reductase and anti-inflammatory agent. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 30(1), 107−113. https://doi.org/10.3109/14756366.2014.892935

Obrosova, I. G., Chung, S. S. M. & Kador, P. F. (2010). Diabetic cataracts: mechanism and management. *Diabetes Metabolism Research and Reviews*, 26(3), 172−180. https://doi.org/10.1002/dmrr.1075

Ohno, R., Ichimaru, K., Tanaka, S., Sugawa H. & Nagai R. (2019). Glucoselysine is derived from fructose and accumulates in the eye lens of diabetic rats. *The Journal of Biological Chemistry*, 24(46), 17326−17338. https://doi.org/10.1074/jbc. RA119.010744

Prnová, M. (2019). Mechanizmy glukózovej toxicity v etiológii diabetickej periférnej neuropatie. *Pokroky vo farmakológii v Slovenskej republike XIV*, recenzovaný zborník vedeckých prác, Univerzita Komenského v Bratislave, s. 5−11. ISBN 978-80-223-5255-0

Reddy, P. Y., Giridharan, N. V. & Reddy, G. B. (2012). Activation of sorbitol pathway in metabolic syndrome and increased susceptibility to cataract in Wistar-obese rats. *Molecular Vision*, 18, 495−503. http://www.molvis.org/molvis/v18/a54

Salmon, J. F. (2020). Kanski's clinical opthalmology. A systematic approach. 9th Edition, Elsevier, Amsterdam, p. 941. ISBN 978-0-7020-7722-1978-0-7020-7712-8

Singh, A. P., Singh, R., Verma, S. S. & Gupta, S. Ch. (2019). Health benefits of resveratrol. Evidence from clinical studies. *Medicinal Research Reviews*, 39(5), 1851−1891. https://doi.org/10.1002/med.21565

Soltesova-Prnova, M., Ballekova, J., Gajdosikova, A., Gajdosik, A. & Stefek, M. (2015). A novel carboxymethylated mercaptotriazinoindole inhibitor of aldose reductase interferes with the polyol pathway in streptozotocin-induced diabetic rats. *Physiological Research*, 64(4), 587−91. https://doi.org/ 10.33549/physiolres.9333034

Shetty, L. L., Harikiran, H. & Sharma, A. (2010). *In vitro* prophylactic cataract prevention study on glucose induced cataract by quercetin and alpha tocopherol. *International Journal of Pharmaceutical Sciences and Research*, 1(7), 41−45.

Sosna, T., Bouček, P., Ernest, J., Hejsek, L., Jirásková, G., Netuková, M., Němec, P., Pelikánová, T., Pěkná, R., Sedláček, K., Studnička, J. & Veith, M. (2016). *Diabetická retinopatie – diagnostika, prevence a léčba*. Axonite, Praha, 279 s., ISBN 978-80-88046-05-9

Studnička, J. (2018). *Onemocnění sítnice a cévnatky v praxi*. Mladá fronta, Praha, 421 s. ISBN 978-80-204-4945-0

Tan, A. G., Kifley, A. & Flood, V. M. (2019). The combination of healthy diet and healthy body weight is associated with lower risk of nuclear cataract in the Blue Mountains Eye Study. *Journal of Nutrition*, 149(9), 1617−1622. https://doi.org/10.1093/jn/nxz103

Tang, W. H., Martin, K. A. & Hwa, J. (2012). Aldose reductase, oxidative stress, and *diabetes mellitus*. *Frontiers in Pharmacology*, 3, Article 87. https://doi.org/10.3389/fphar.2012.00087

Xu, J., Qiuli, F., Chen, X. & Yao, K. (2020). Advances in pharmacotherapy of cataracts. *Annals of translational medicine*, 8(22), 1552. https://doi.org/10.21037/atm-20-1960

Yamakoshi, J., Saito, M., Kataoka, S. & Tokutake, S. (2022). Procyanidin-rich extract from grape seeds prevents cataract formation in hereditary cataractous (ICR/f) rats. *Journal of Agricultural and Food Chemistry*, 50(17), 4983−4988. https://doi.org/10.1021/jf0201632

Yan, L. (2012). Redox imbalance stress in *diabetes mellitus*: Role of the polyol pathway. *Animal Models and Experimental Medicine*, 1(1), 7−13.

World report on vision. (2019). World Health Organization (WHO), p. 180. ISBN 9789241516570

Wong, M. Y. Z., Man, R. E. K., Gupta, P. & Chong, M. F. (2018). Dietary intake and diabetic retinopathy: A systematic review. *PLoS ONE*, 13(1), e0186582 https://doi.org/10.1371/journal.pone.0186582

Wu, Y., Tang, L. & Chen, B. (2014). Oxidative Stress: Implications for the Development of Diabetic Retinopathy and Antioxidant Therapeutic Perspectives. *Oxidative Medicine and Cellular Longevity*, 752387. https://doi.org/10.1155/2014/752387