



DIABETIC RETINOPATHY AND NATURAL ANTIOXIDANTS: A SYSTEMATIC REVIEW

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Abstract: Diabetes mellitus is a chronic disease that can result in both macrovascular and microvascular complications. Diabetic retinopathy is one of the most common microvascular complication of diabetes mellitus. Epidemiologically number of adults worldwide with DR, and vision-threatening DR was estimated to be 103.12 million, and 28.54 million respectively. The prevalence of diabetic retinopathy will betwice as much by 2045 as the current statistics. Since DR is a chronic disease and pharmacological treatment will help the patient's health by slowing down the disease progression. In this systematic review, we have focused on the efficacy of combination national therapy of both pharmacological and herbal antioxidants in diabetic retinopathy. To study a correlation between diabetic retinopathy and natural antioxidants. The systematic review includes two databases PubMed and google scholar for reference data. The data extraction is based on PRISMA guidelines. Supplements irrespective of trace quantity also showed remarkable role. Curcumin, Vitamins, and Zinc are discussed in this systematic review. This systematic review concluded the results in which curcumin emerges to be the best antioxidant with specific characteristics and low adverse drug reactions. Others such as vitamins, Zinc also provide adequate antioxidant properties. Supplementation is often beneficial and necessary if dietary intake is below recommended guidelines. Overall, it was observed that herbal antioxidants are the choice of non-pharmacological treatment.

Index Terms - Diabetes, Diabetic Retinopathy, Herbal antioxidants, Turmeric, PRISMA, Vitamins

I. INTRODUCTION

Diabetic retinopathy (DR) is one of the most specific microvascular consequences of diabetes mellitus (DM) and is the leading cause of preventable blindness in working-aged persons. Diabetic Retinopathy results in injured blood vessels in light-sensitive tissue located at the back of the retina.¹

In the year 2020, the number of adults worldwide with DR, and vision-threatening DR was estimated to be 103.12 million, and 28.54 million respectively. A hike in the patient count will be observed in 2045. This count will be approximately 2 times the current statistics one in five people living with diabetes in India have a certain form of DR (13 million in India) and one in ten (6.5 million) has a vision-threatening form of DR.²

The best way to treat diabetic retinopathy and associated angiogenic consequences is with intravitreal injections of anti-VEGF medications. The monoclonal antibody ranibizumab (Lucentis[®]), the long-acting antibody bevacizumab (Avastin[®]), the aptamer pegaptanib (Macugen[®]), and the recombinant fusion protein aflibercept (Eylea[®]) are the anti-VEGF agents most frequently used to treat diabetic retinopathy.³

The clinical investigation involves direct physical examination by an ophthalmologist, and imaging techniques such as fundus photography or optical coherence tomography are confirmatory investigational parameters for Diabetic retinopathy. ETDRS separates fine detailed DR characteristics using multiple levels. This type of grading is done upon all seven retinal fundus Fields of View (FOV). Although ETDRS is the gold standard, due to implementation complexity and technical limitations, alternative grading systems are also used such as the International Clinical Diabetic Retinopathy (ICDR) scale which is accepted in both clinical and Computer-Aided Diagnosis (CAD) settings.⁴

For this purpose, fine pathognomonic DR signs in the initial stages are determined normally, after dilating pupils (mydriasis). Then, DR screening is performed through slit-lamp biomicroscopy with a + 90.0 D lens and direct/indirect ophthalmoscopy. The next step is to diagnose DR which is done by finding DR-associated lesions and comparing them with the standard grading system criteria. Currently, the diagnosis step is done manually⁵ Prediabetes is defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), which is characterized by hyperglycemia, insulin resistance, and β -cell dysfunction. Disease progression includes various microvascular and macrovascular complications like cardiovascular disease, stroke, peripheral artery disease, retinopathy, neuropathy, and nephropathy. Recent research has shown too much attention to phytochemicals and the antioxidant trace elements to treat and control some diseases which include T2DM, prediabetes, metabolic syndrome, CVD, and chronic venous insufficiency (CVI).⁶ Oral Antioxidant Supplements have a significant influence on ocular health. Certain vitamins may prevent or slow the risk of several eye diseases like age-related macular degeneration (AMD), glaucoma, diabetic retinopathy (DR), and cataracts.⁷

Constant solar radiation exposure can result in eye damage by first destroying the cornea, anterior chamber, lens & vitreous body to the retina which further leads to cornea addition to causing DNA damage, ultraviolet (UV) light can also cause photo-oxidative stress through the production of reactive oxidative species (ROS). ROS leads to cell damage and aging, resulting in corneal degeneration, lens opacification (cataracts), and the occurrence of eye diseases, including various retinal and optic nerve degenerative diseases, such as glaucoma and age-related macular degeneration (AMD).⁸

Natural Antioxidants Supplementation:

It is postulated that antioxidants inhibit abnormal metabolism and slow DR progression by inhibiting the production of ROS, neutralizing free radicals, and augmenting the antioxidant defense system. Oral supplementation with natural antioxidants carries the great advantage of being a non-invasive treatment with presumably no harmful effects. Oral supplementation with natural antioxidants carries the great advantage of being a non-invasive treatment with presumably no harmful effects.^{9,21-23}

Curcumin:

It is an active ingredient contained in the rhizome of the *Curcuma longa* plant of turmeric. Curcumin is the principal curcuminoid found in turmeric (*Curcuma longa* Linn.), a popular spice in Asian cuisine whose beneficial effects on glycemic control have been used in ayurvedic and traditional Chinese medicine for thousands of years.^{10,11}

Various research studies involved different pharmacological actions of curcumin in the treatment of diabetic retinopathy. Curcumin possesses four basic indications such as antioxidants, anti-inflammatory, inhibition of VEGF, and activating PPAR (Peroxisome Proliferation -activate receptor), which reduces the glycemic level, thus preventing diabetic retinopathy. The utility of curcumin proves to be more economic and effective than allopathic treatments such as anti-inflammatory and antiangiogenic drugs which are costly and resulted in adverse side effect in retinal tissue. Curcumin also possesses an antiangiogenic effect reduces inhibits the elevated VEGF level in the retina and abolish IL-18 induced increase in VEGF production.¹²

Relationship between Curcumin and transcription factor

In reference to genetics, DR is also generated from the activation of EGR-1. Preclinical findings in support of the curcumin effect have shown downregulated the expression of EGR-1. A strong optimistic approach is developed for the involvement of curcumin in the control of Gene action. Specific characteristics of being economics, easy availability, no deleterious effect, turmeric, and its constituents, curcumin is the cornerstone in the control of Diabetic Retinopathy.¹³

Correlation between Vitamins & Diabetic Retinopathy

Numerous experimental studies have shown that different vitamins (B1, B12, C, D, E, folate), lipoic acid, lutein, and n-Acetyl cysteine betaine can improve visual acuity.

Vitamin B1(Thiamine)

Serum thiamine level regulated the hyperglycemic level by generating a halt in polyol pathway activation. Therapeutically thiamin also protects the vascular endothelium from advanced glycation end-product injury.¹³

Vitamin B2 (Riboflavin)

Intake of Riboflavin is efficacious in patients with diabetic retinopathy. Riboflavin develops a shielding effect in the treatment of diabetic retinopathy by reducing oxidative stress, and hyperglycemia and preventing homocysteine-induced injury. According to the murine model, riboflavin also enhances BDNF expression. BDNF is neuroprotective which is higher in Prediabetic patients rather than diabetic.¹³

Vitamin B6 (Pyridoxal 5'Phosphate)

Vitamin B6 is available in several forms, available forms, among them P5P is the natural active form. Vitamin B6 acts as a cofactor for various metabolic activities such as one-carbon cycle methylation and homocysteine metabolism. An inadequate amount of Vitamin B6 can contribute to pancreatic islet cell autoimmunity resulting in Type1 diabetes. Intake of P5P may lower the risk of developing diabetes and diabetic retinopathy.¹³

Vitamin B9 (Folate)

A-methyl folate and methyl cobalamin both reduce homocysteine efficiency. Lowering homocysteine levels with folate supplements will enhance blood flow and perfusion combining alpha methyl folate with B2, B6(P5P)and B12 will be safe and economical supplements to reduce and reverse diabetic retinopathy.¹³

Vitamin D

Vitamin D Supplements are beneficial in patients with both Types (I& II) diabetes. According to research 1,25, dihydroxy vitamin D triggers the release of insulin by activating Pancreatic beta cells.¹³

Vitamin C (ascorbic acid):

It is an essential micronutrient in humans and is required for several important biological functions via acting as an enzymatic cofactor and reducing agent. Ascorbic acid is water-soluble and essential for regenerating other antioxidants such as vitamin E and glutathione. In a research study conducted by Longo-Mbenza et al., the mean serum level of vitamin C in patients with DM was shown to be significantly lower than in those without DM. There is some evidence to suggest that people with type 2 diabetes mellitus (T2DM) have lower plasma vitamin C concentrations compared to those with normal glucose tolerance (NGT). It also produces beneficial effects on endothelial integrity which would result in improving endothelial dysfunction.¹⁴

Vitamin E

It is a peroxy radical scavenger, which quenches free radicals and reduces retinal oxidative stress in the retina. Thus, preventing the attack of free radicals in diabetic retinopathy patients.¹⁵

Zinc:

Metanalysis of different clinical trial studies concluded that zinc despite trace elements proves to be beneficial in Diabetic retinopathy patients. Zinc possesses antioxidant properties through two main mechanisms. First protection of protein sulfhydryl groups from free radicals. Secondly reduction of free radical formation through the antagonism of redox-active transition metals such as iron and copper.¹⁶

2.0. MATERIAL AND METHODS

Eligibility Criteria

Eligibility criteria describe characteristics that must be shared by all participants. It can be divided into two forms: Exclusion criteria and Inclusion criteria.

Exclusion Criteria

We will exclude the studies including preclinical, pediatric population, lactating females, other eye disorders: Glaucoma and Conjunctivitis, and duplicate records.

Inclusion Criteria

We will include the studies which fulfill the criteria for diabetic patients and in which glycemic index is in the normal range.

2.1.Evidence Synthesis:

Databases used to identify the most relevant papers included PubMed and Google Scholar. Search keywords used in different forms included “prediabetes”, “diabetic retinopathy”, and “oral antioxidant supplementation”. Articles published in the last five years (2016-23). In total, 13167 studies were identified during the primary search from scientific databases. After removing duplicate records, 7828 studies were left. After applying exclusion criteria 341 records were left. Finally, 50 records were identified on basis of inclusion criteria.

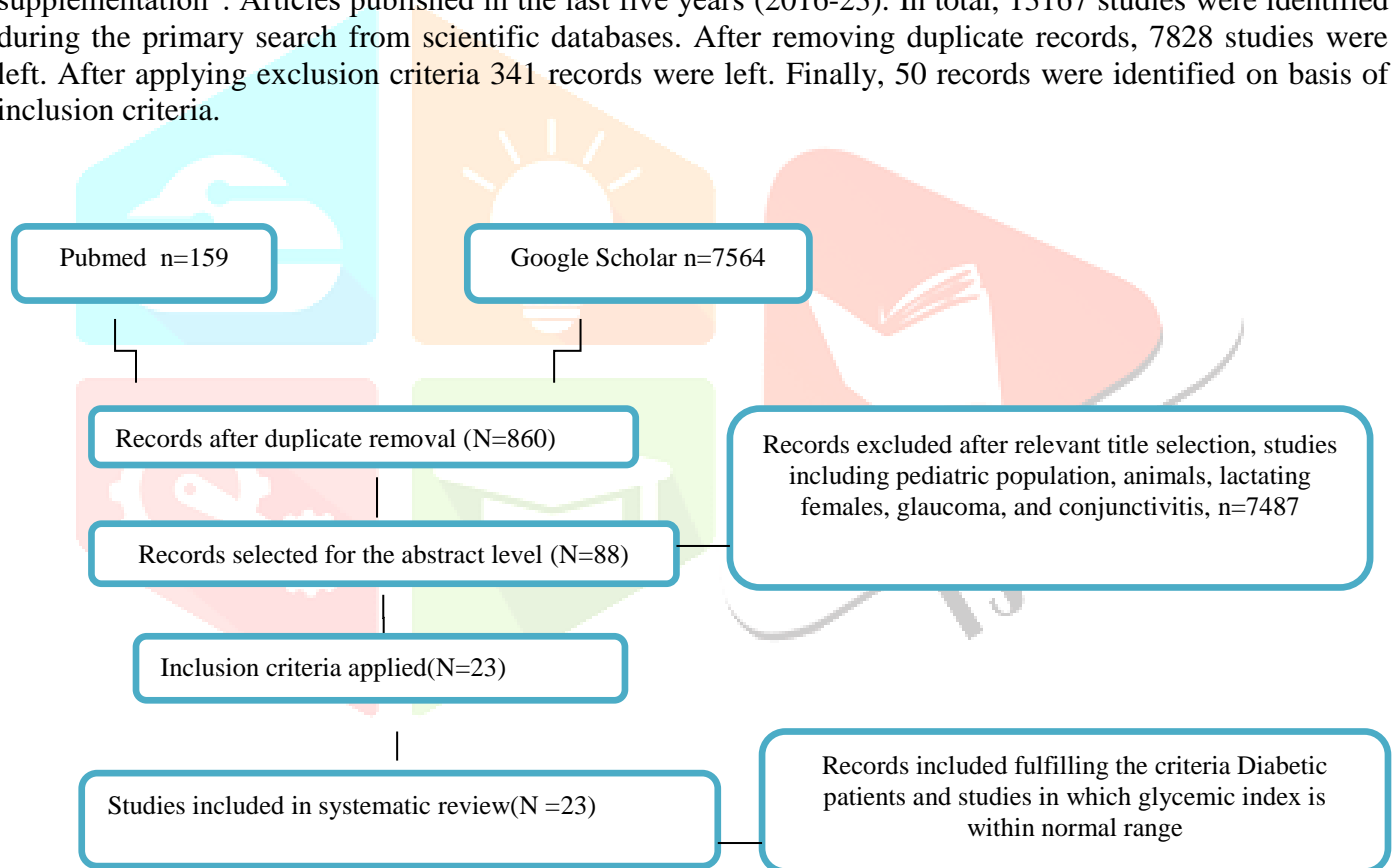


Fig 1: Studies selection according to PRISMA

3.0. Results and Discussion

Diabetic retinopathy is a microvascular complication of diabetes. Various Pharmacological treatments are available including anti-VEGF drugs like Ranibizumab and Bevacizumab¹⁷. Non-pharmacological antioxidant supplements also play a vital role in the prevention and progression of the disease.¹⁸ The current systematic review evaluated various research studies and clinical trials to discuss the most efficacious antioxidants. Curcumin with its specific characteristics is the best antioxidant for Diabetic retinopathy. Fundamental indications include antioxidants, anti-inflammatory, and antiangiogenic¹⁹In diabetic retinopathy antiangiogenic action of curcumin inhibits the elevation of VEGF levels in the retina. Curcumin hinders the activation of EGR-1,by down regulation of EGR-1.In diabetic retinopathy, impaired endothelial functions are improved with different vitamin supplements.²⁰ Ideally all vitamins prove useful for the disease. Vitamin B1, B2, B6, B9, Vitamin C, Vitamin D, and Vitamin E are the most advantageous among all. Vitamin B1 regulates polyol pathway activation which is responsible for hyperglycemia

hyperhomocysteinemia²¹. Vitamin B6 maintains the immunity of islet cells. Vitamin B9 acts by lowering homocysteine levels which will enhance blood flow and perfusion. Vitamin D&E, glutathione is also available with specific antioxidants property.²² Supplements including Zinc and flavonoids despite trace quantity show the remarkable antioxidant property. Supplementation is often beneficial and necessary if dietary intake is below recommended guidelines.²³

3.1. Conclusion

The utility of Non-Pharmacological supplements is observed in the above systematic review. Intake of natural antioxidants by Diabetic retinopathy patients manifests the beneficial effect. Among various natural antioxidants, curcumin proves to be the best choice for DR patients. Researchers conduct various large-scale studies to generate supportive information regarding curcumin's utility in diabetic retinopathy patients. Other antioxidants including vitamins, Zinc, and flavonoids also possess satisfactory activity in diabetic retinopathy. Nutrition sources of such antioxidants are available from both plants and animals

Declaration of Competing Interest

The authors declare that they have no known competing financial interests that could have appeared to influence the work reported in this paper.

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Conflict of Interest

There are no conflicts of interest.

REFERENCES

1. Nentwich MM, Ulbig MW. Diabetic retinopathy - ocular complications of diabetes mellitus. *World J Diabetes*. 2015 Apr 15;6(3):489-99. doi: 10.4239/wjd.v6.i3.489.
2. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, Bikbov MM, Wang YX, Tang Y, Lu Y, Wong IY, Ting DSW, Tan GSW, Jonas JB, Sabanayagam C, Wong TY, Cheng CY. Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045: Systematic Review and Meta-analysis. *Ophthalmology*. 2021 Nov;128(11):1580-1591. doi: 10.1016/j.ophtha.2021.04.027.
3. Osaadon P, Fagan XJ, Lifshitz T, Levy J. A review of anti-VEGF agents for proliferative diabetic retinopathy. *Eye (Lond)*. 2014 May;28(5):510-20. doi: 10.1038/eye.2014.13.
4. Salz DA, Witkin AJ. Imaging in diabetic retinopathy. *Middle East Afr J Ophthalmol*. 2015 Apr-Jun;22(2):145-50. doi: 10.4103/0974-9233.151887.
5. Dwyer AE. and Henriksen ML, Equine Ocular Examination and Treatment Techniques, *Equine Ophthalmology*, doi: 10.1002/9781119782285, (1-89), (2022).
6. Lawal Y, Bello F, Kaoje YS; Prediabetes Deserves More Attention: A Review. *Clin Diabetes*. 2020 Oct 1; 38 (4): 328–338. <https://doi.org/10.2337/cd19-0101>
7. Ravi K, Jose R, Sumitha SK, Johny T, Krishnaveni K, Sundaram RS, Ramanathan S. An Overview of Treatment Challenges and the role of Herbal Antioxidants in Diabetes Mellitus. *Research J. Pharm. and Tech*. 2017; 10(8): 2765-2770. doi: 10.5958/0974-360X.2017.00490.5
8. Mahendra CK, Tan LTH, Pusparajah P, Htar TT, Chuah LH, Lee VS, Low LE, Tang SY, Chan KG, Goh BH. Detrimental Effects of UVB on Retinal Pigment Epithelial Cells and Its Role in Age-Related Macular Degeneration. *Oxid Med Cell Longev*. 2020 Aug 12;2020:1904178. doi: 10.1155/2020/1904178.
9. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. *Sultan Qaboos Univ Med J*. 2012 Feb;12(1):5-18. doi: 10.12816/0003082.

10. Badmanaban R, Saha D, Sen DJ, Biswas A, Mandal S, Basak S. Turmeric: A holistic Solution for Biochemical malfunction. *Research Journal of Pharmacy and Technology* 2021 Oct; 14(10):5540-0. doi: 10.52711/0974-360X.2021.00966
11. Ehrlich, S.D. (2014). Turmeric. Retrieved from <http://www.umm.edu/health/medical/altmed/herb/turmeric>
12. Marton LT, Pescinini-E-Salzedas LM, Camargo MEC, Barbalho SM, Haber JFDS, Sinatora RV, Detregiachi CRP, Girio RJS, Buchaim DV, Cincotto Dos Santos Bueno P. The Effects of Curcumin on Diabetes Mellitus: A Systematic Review. *Front Endocrinol (Lausanne)*. 2021 May 3;12:669448. doi: 10.3389/fendo.2021.669448.
13. Shi C, Wang P, Airen S. et al. Nutritional and medical food therapies for diabetic retinopathy. *Eye and Vis* 7, 33 (2020). <https://doi.org/10.1186/s40662-020-00199-y>
14. Kumar SB, Dhanraj M. Role of Vitamin C in Body Health. *Research J. Pharm. and Tech* 2018; 11(4): 1378-1380. doi: 10.5958/0974-360X.2018.00257.3
15. Stoyanavsky DA, Goldman R, Darrow RM et al., Endogenous ascorbate regenerates vitamin E in the retina directly and in combination with exogenous dihydrolipoic acid. *Curr Eye Res*. 14;1995:181-9.
16. Mohammadi SM, Cheraghian B, Azhdari M et al., The effect of curcumin and zinc co-supplementation on glycemic parameters in overweight or obese prediabetic subjects: A phase 2 randomized, placebo-controlled trial with a multi-arm, parallel-group design. *Phytotherapy Research*. 2021;1-11
17. Chatziralli I. Ranibizumab for the treatment of diabetic retinopathy. *Expert Opin Biol Ther*. 2021 Aug;21(8):991-997. doi: 10.1080/14712598.2021.1928629.
18. Alfonso-Muñoz EA, Burggraaf-Sánchez de Las Matas R, MataixBoronat J, Molina Martín JC, Desco MC. Role of Oral Antioxidant Supplementation in the Current Management of Diabetic Retinopathy. *Int J Mol Sci*. 2021 Apr 13;22(8):4020. doi: 10.3390/ijms22084020.
19. Das A, Roy A, Kumar RS et al. Anti-inflammatory Activity of Turmeric Oil Mediated Silver Nanoparticles. *Research J. Pharm. and Tech*. 2019; 12(7):3507-3510. doi: 10.5958/0974-360X.2019.00596.1
20. Bunin AI, Filina AA, Elichev VP. A glutathione deficiency in open-angle glaucoma and the approaches to its correction. *VestnOftalmol*. 108;1992:13-5
21. Lassen N, Black WJ, Estey T et al. The role of crytallins in the cellular defense mechanisms against oxidative stress. *Sem Develop Biol*. 19;2008:100-112
22. Suresh PK, Sah AK, Daharwal SJ. Role of free radicals in ocular diseases: An overview. *Research J. Pharm. and Tech*. 7(11): Nov. 2014 Page 1330-1344
23. Hulse JD et al: Carnitine biosynthesis-beta hydroxylation of trimethyllysine by an α -keto glutarate dependent mitochondrial dioxygenase. *J Biol Chem*. 1978, 253: 1654-1659