International Journal of Pharmacological Research
ISSN: 2277-3312
www.ssjournals.com
Journal DOI:10.7439/ijpr

A review: Cataract, a common ocular complication in Diabetes

Mital Bhadania[*1] and Falguni Majmudar[2]

[1]*Department of Product Development, McLeon Pharmaceuticals, Gandhinagar, India.*
[2] *Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad, India.*

Corresponding author*
Mital Bhadania
Department of Product Development,
McLeon Pharmaceuticals, Gandhinagar, India.
E-mail: mitalbhadania@yahoo.com

Abstract

With increasing prevalence of diabetes and its associated complications is a priority of health service globally. Diabetic ocular complications are most common in both type-1 and type-2 diabetes, considering the fifth most common cause of legal blindness. According to WHO, cataract is 33% of all type of visual impairment. Simply diabetic cataracts are characterized by cortical or posterior subcapsular opacities. Aldose reductase and polyol are responsible for diabetes ocular complications. Intracellular accumulation of sorbitol leads to osmotic stress resulting in the formation of lens opacities. Several clinical studies investigated the role of phacoemulsification surgery and its post surgery complications. Researchers are trying to develop aldose reductase inhibitors and antioxidants, may be effective treatment to prevent or cure diabetes cataract.

Keywords: Diabetes mellitus, Cataract, Aldose Reductase, Polyol Pathway, Sorbitol.

1. Introduction

Addressing the increasing prevalence, and associated disease burden, of diabetes is a priority of health services internationally. The global diabetes epidemic is a major public health challenge worldwide, and one of the greatest contributors to the global burden of disease, with an estimated 65% increase in diabetics by 2025, to 380 millions [1, 2].

Diabetes is a well-recognized cause of premature death and disability, increasing the risk of cardiovascular disease, kidney failure, blindness and lower-limb amputation [3]. Hyperglycemia, blood lipids and blood pressure has been three major factors to be considered for diabetes complication and disease progression [4, 5]. A frequent complication of both type 1 and type 2 diabetics is diabetic ocular complications, which is considered the fifth most common cause of legal blindness. In 95% of type 1 diabetic and 60% of type 2 diabetics with disease duration longer than 20 years, signs of diabetic retinopathy occur [6-8].

Cataract is considered a major cause of visual impairment in diabetic patients as the incidence and progression of cataract is elevated in patients with diabetes mellitus [4, 5]. The association between diabetes and cataract formation has been shown in clinical epidemiological and basic research studies. Globally, Cataracts occur remain the leading cause of blindness, affecting approximately 18 million people. Cataracts occur at an earlier age and 2-5 times more frequently in patients with diabetes, thus the visual loss has a significant impact on the working population [9-11].

According to World Health Organization, cataract is 33% of all type of visual impairment. Overall, up to 20% of all cataract procedures are estimated to be performed for diabetic patients [12]. Rate of cataract and cataract surgery is high as cataract is most common cause of visual impairment.

Cataract surgery most common ophthalmic procedure worldwide, but main aim to delay or prevent the development of cataract in diabetes patients remains a challenge. Particularly in developing countries, both diabetes and cataract become health and economic burden, where diabetes treatment is insufficient and cataract surgery often inaccessible [13].

In this review, understanding of the pathophysiological significance of aldose reductase are presented that would be relevant to diabetic cataract. An extensive review on the pathogenesis of diabetes complications is outside the scope of this review.

2. Ocular complication in Diabetes

Diabetes is metabolic disorder affecting many organs including eye. Diabetes cataracts are characterized by cortical or posterior sub capsular opacities, and in adults the opacities are known to be an acceleration of age related cataracts [14]. Intensive control of blood glucose and systemic hypertension reduces the risk of new onset diabetic retinopathy and slow the progression of existing diabetic retinopathy. Studies related to cataract formation in diabetic

patients have shown that hyperglycemia is associated with loss of lens transparency in a cumulative manner. Hyperglycemia may induce temporary lens opacification and swelling as well as transient hyperopia. It has been suggested that rapid glycemic control can irreversibly increase lens opacities [15, 16].

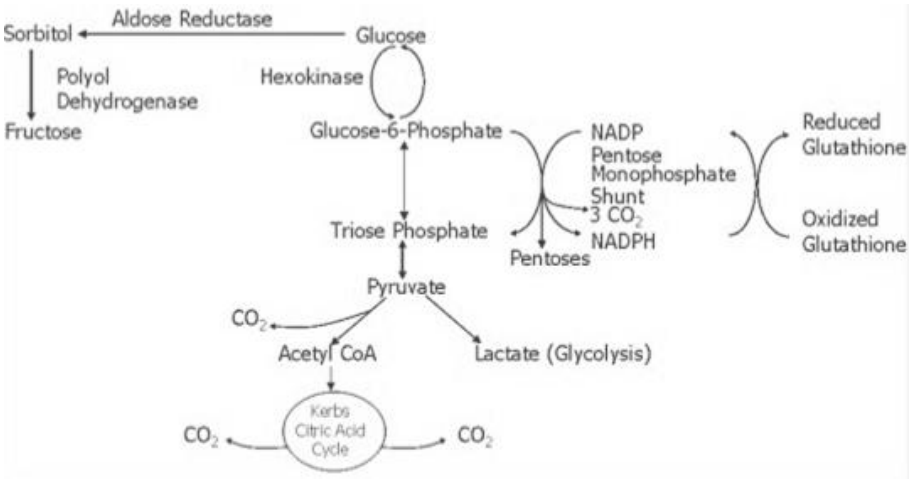
3. Risk factors for cataract in diabetes

Cataract can be considered as an earliest complication of diabetes mellitus. Diabetic patients are 2-5 times more prone to develop cataract than non diabetics and risk may reach 15-25 times in diabetics less than 40 years of age [10, 16].

4. Pathogenesis of diabetic cataract

If large amounts of glucose are present in blood (as in diabetes mellitus), hexokinase becomes saturated and the excess glucose enters the polyol pathway when aldose reductase (AR) reduces it to sorbitol illustrated in Fig. 1.

Fig: 1 Polyol Pathway



Aldose reductase is a cytosolic enzyme present in most of the mammalian cells, although the distribution of the enzyme is not uniform among tissues. Around 60 years ago the polyol pathway was first identified in the seminal vesicle by Hers [17], who demonstrated the conversion of blood glucose in to fructose, an energy source of sperm cells. The presence of diabetic rat lens demonstrated by Van Heyningen [18].

Later researcher has opening a new way concerning the pathological role of aldose reductase and the polyol pathway in the development of diabetes complications on eye, kidney and nerve. Since those days, inhibition of aldose reductase has been expected to become a potential therapy for diabetes and its complications. However, it is necessary to understand the pathological and physiological role of the polyol pathway in contrast of possible side effect of long term inhibition of aldose reductase in diabetic patients.

Intracellular accumulation of sorbitol leads to osmotic changes resulting in hydropic lens fibers that degenerate, ultimately results in the formation of lens opacities (form sugar cataracts). The speed of conversion sorbitol is faster than it is converting to fructose by the enzyme sorbitol dehydrogenase. These findings have led to the "Osmotic Hypothesis" of sugar cataract formation, emphasizing that the intracellular increase of fluid in response to AR-mediated accumulation of polyols results in lens swelling associated with complex biochemical changes ultimately leading to cataract formation [19-21].

According to the "osmotic stress" hypothesis, diabetic cataracts are the consequence of swelling of lens epithelial cells caused by accumulation of osmotically significant amounts of polyol. Swelling of epithelial cells then initiates a cascade of metabolic imbalances culminating in rupture of epithelial cells and formation of cataracts. The osmotic hypothesis is based primarily on two lines of evidence:

1. The accumulation of millimolar concentrations of sorbitol in the lens of diabetic
2. Elevation of the osmolarity of incubation media prevents a variety of metabolic abnormalities in lenses incubated at elevated glucose levels in vitro.

While the osmotic hypothesis is consistent with a considerable body of experimental data on the lens, its role in the pathogenesis of diabetic cataracts is questioned, and it is generally considered to be untenable as an explanation for the pathogenesis of diabetic complications in most other tissues in which sorbitol concentrations never exceed the micromolar range and in which no evidence of cellular swelling is evident by electron microscopy [22].

Studies showed that transgenic hyperglycemic mice over expressing AR and phospholipase D (PLD) genes

became susceptible to develop diabetic cataract in contrast to diabetic mice over expressing PLD alone, an enzyme with key functions in the osmotic regulation of the lens [23].

These findings show that impairments in the osmotic regulation may render the lens susceptible to even small increases of AR mediated osmotic stress, potentially leading to progressive cataract formation.

Type 1 diabetic patient more susceptible to rapid cataract formation due to the extensive swelling of cortical lens fibers [24]. Person under 60 years of age having short duration of diabetes were positively correlated with the prevalence of posterior subcapsular cataracts [25].

It has been proven that the polyol pathway is the primary mediator of diabetes induced oxidative stress in the lens. Researcher has focus on first step of polyol pathway as initiating factor in diabetic cataract formation.

The fact behind this, accumulation of sorbitol induced stress as osmotic stress in the endoplasmic reticulum (ER), main site of protein synthesis, leads to generation of free radicals. ER stress may be due to glucose level disturbance initiating an unfolded protein response that generates reactive oxygen species that cause oxidative stress damage to lens fibers [26, 27].

There are number of publications are describing oxidative stress damage to the lens fibers, but not any particular evidence that these free radicals initiating or increasing lens opacity. Studies showed that increase level of free radical like hydroxyl (OH-) or nitric oxide (NO-) free radical, may lead to an increased peroxynitrite formation, which leads to cell damage due to its oxidizing properties [28, 29]. Moreover, increase level of glucose in the aqueous humor may leads to glycation of lens protein, resulting generation of superoxide radicals (O2-) [30].

One side increase level of free radicals and another side loss of antioxidants by glycation and inactivation of antioxidants enzymes like superoxide dismutase, which is important for degradation of superoxide radicals (O2-) into hydrogen peroxide (H2O2) and oxygen, finally minimize the protective effect of superoxide dismutase in the presence of diabetes mellitus has been shown in various in vitro and in vivo animal studies [31-33].

In conclusion, initiating mechanism in diabetic cataract formation is the polyol pathway and increased osmotic stress in the lens fibers resulting its swelling and rupture.

5. Surgery as Solutions for cataract

While there is no way to prevent cataracts, there are only things to slow their formation. Modifiable factors that increase the risk of cataract include smoking, high blood pressure, obesity, excessive alcohol intake, and last but not least blood glucose level.

In the beginning stages of cataracts, vision may be slightly improved using forms of visual correction. However, in the later stages, surgery is required. Fortunately, surgery has proven to be extremely successful in the removal of cataracts.

There are two main type of surgical procedure using throughout the world. One is phacoemulsification (Phaco) and second involves two different types of extracapsular cataract extraction (ECCE). In most surgery intraocular lens is incerted. ECCE utilises a larger incision (10-13mm) and therefore usually requires stitching, and this in part led to the modification of ECCE known as manual small incision cataract surgery (MSICS). Cataract extraction using intracapsular cataract extraction (ICCE) has been superseded by phaco & ECCE, and is rarely performed [34, 35].

Phacoemulsification is the most commonly performed cataract procedure in the developed world. However, the high cost of a phacoemulsification machine and of the associated disposable equipment means that ECCE and MSICS remain the most commonly performed procedure in developing countries.

5.1 Phacoemulsification

Phacoemulsification is most popular and preferred technique in most types of cataract, developed by kelman in1967 and was not widely accepted until 1996 [36]. Later it can be taught safely and effectively to residents with no cataract surgery experience as a primary surgeon [35].

Patients with diabetes may have poorer vision outcomes than those without diabetes. Surgery may cause rapid acceleration of retinopathy, induce rubiosis or lead to macular changes [37, 38]. Even uncomplicated cataract surgery may induce postsurgical inflammation and vitreous instability that may subsequently cause postoperative macular edema in normal individuals.

Several clinical studies investigated the role of phacoemulsification cataract surgery on the progression of macular edema and diabetic retinopathy. Macular edema is a well-known complication after cataract surgery. When the post cataract macular edema is associated with a decrease in visual acuity, it can be categorized as clinical pseudophakic cystoid macular edema.

Diabetic retinopathy has long been implicated as a risk factor for more prominent postoperative macular edema and poorer visual outcomes. In eyes with diabetic retinopathy, the blood-retina barrier is often impaired to a variable degree, which may cause the eyes to be more prone to develop postoperative macular edema. The incidence of post

phacoemulsification macular edema in diabetic retinopathy has been reported to range from 31% to 81%, which is much higher than the incidence of post phacoemulsification in non-diabetic patients [39].

Studies showed that phacoemulsification surgery severly affects the blood aqueous barrier in diabetic patients with proliferative diabetic retinopathy than non diabetic patients [40].

A study on diabetic beneficiaries (n=139759) from 1997 to 2001 showed that the rate of cystoids macular edema formation after cataract surgery in diabetic patients is significantly higher than non diabetic patients [41].

Diabetic eyes have a high incidence 22% of increased center point thickness on optical coherence tomography as macular edema after cataract surgery. Treatment to prevent this might improve outcomes in similar individuals after surgery [42].

Wielders *et al* to evaluate the optimum medical strategy to prevent cystoid macular edema (CME) after cataract surgery showed topical NSAIDs significantly reduced the odds of developing CME, as compared to topical corticosteroids, in non-diabetic and mixed populations. A combination of topical NSAIDs and corticosteroids reduced the odds of developing CME in non-diabetic and diabetic patients, as compared to topical corticosteroids [43].

6. Cataract treatment

Cataract is a visual impairment caused due to opacification or optical dysfunction of crystallin lens affecting more than 17 million people around the world. Even though the incidences of cataract are increasing day by day among the elderly persons but, still except surgery no other ways of treatment have been successfully developed so far [44].

6.1 Aldose reductase inhibitors.

Researcher has continuing to trying from natural and synthetic way to prevent or cure diabetic cataract. Studies on natural products with known aldose reductase activity e.g. Flavanoid extract of *Vernonia Cinerea* [45], *Caesalpinia pulcherrima* [46], Nobiletin, one of the most abundant polymethoxyflavones in citrus peel [47], glycoside and lignin extract of *Cornus Officinalis* [48], ethanolic extract of *Chromolaena Odorata* [49], *Foeniculum vulgare* Mill [50], *Pterocarpus marsupium* bark [51], *Ocimum sanctum*, *Withania somnifera, Curcuma longa*, and *Azadirachta indica* [52, 53].

Nonsteroidal anti inflammatory drugs, such as sulindac, aspirin or narproxen have been reported to delay cataract in diabetic rats through a aldose reductase activity [43, 54-58].

Several experimental studies has been reported the role of aldose reductase inhibitor in prevent or delaying diabetic cataract formation in animal models. Renirestat, Fidarestat, Kenostat, Alrestatin, Imrestat, Ponalrestat, Epalrestat, Zenarestat, and Minalrestat have been support to prevent diabetic cataract animal model. These studies provide a rationale for a potential future use of ARI in the prevention or treatment of diabetic cataracts [59].

6.2 Antioxidant treatment of diabetic cataract

It has been discussed earlier that the polyol pathway is the primary mediator of oxidative stress in the lens, resulting cataract formation.

The antioxidant alpha lipoic acid has been shown to be effective in prevent and delaying diabetic cataract in adult SD rats [60, 61].

Yoshida *et al*. demonstrated that the treatment with vitamin E protect from cataract in animal studies [62], but the study on 1193 human subject, Vitamin E given for 4 years at a dose of 500 IU daily did not reduce the incidence of or progression of nuclear, cortical, or posterior subcapsular cataracts. These findings do not support the use of vitamin E to prevent the development or to slow the progression of age-related cataracts [63].

Post translational modifications in lens crystallins due to glycation and oxidation have been suggested to play a significant role in the development of cataracts associated with aging and diabetes. Pyruvate, alpha keto acids can protect the lens against fructose mediated damage to lens alpha crystalline due to oxidative damage [64].

Conflicts of interest: 'Conflicts of interest: none'

References

[1] World Health Organization. Global Status Report on Noncommunicable Diseases, 2014n. Available from http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_ eng.pdf?ua=1 accessed May 26, 2015.

[2] R. Dobson, R. Whittaker, Y. Jiang *et al*. Text message-based diabetes self-management support (SMS4BG): study protocol for a randomised controlled trial. *Trials.* 2016; 17: 1-10.

[3] B. Levitan, Y. Song, E. Ford *et al*. Is nondiabetic hyperglycaemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch. Intern. Med*. 2004; 164: 2147–55.

[4] J. Harding, M. Egerton, R. van *et al*. Diabetes, glaucoma, sex, and cataract: analysis of combined data fromtwo case control studies. *British. J. Ophthalmol*. 1993; 77: 2–6.

[5] H. Kahn, H. Leibowitz, J. Ganley *et al*. The Framingham eye study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham heart study. *Am. J. Epidemiol.* 1977; 106: 33–41.
[6] P. Guillausseau, P. Massin, M. Charles, *et al*. Glycaemic control and development of retinopathy in type 2 diabetes mellitus: a longitudinal study. *Diabetic Medicine*. 1998; 15: 151–55.
[7] R. Turner. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*. 1998; 352 (9131): 837–53.
[8] I. Stratton, E. Kohner, S. Aldington *et al*. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001; 44 (2): 156–63.
[9] World Health Organization. http://www.who.int/topics/cataract/en/ Accessed 7 April 2016.
[10] B. Klein, R. Klein, S. Moss. Incidence of cataract surgery in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Am. J. Ophthalmol*. 1995; 119: 295–300.
[11] B. Klein, R. Klein, Q. Wang *et al*. Older-onset diabetes and lens opacities. The Beaver Dam Eye Study. *Ophthalm. Epid.* 1995; 2: 49-55.
[12] A. Hamilton, M. Ulbig, P. Polkinghorne. Epidemiology of diabetic retinopathy. In: Hamilton AM, Ulbig MW and Polkinghorne P Management of Diabetic Retinopathy. London*: BMJ Publishing Group.* 1996: 1-15.
[13] G. Tabin, M. Chen, L. Espandar. Cataract surgery for the developing world. *Curr. Opin. Ophthalmol*. 2008; 19(1): 55–59.
[14] J. Harding. Recent studies of risk factors and protective factors for cataract. *Curr. Opin. Ophthalmol*. 1997; 8: 46–49.
[15] S. Kato, A. Shiokawa, H. Fukushima *et al*. Glycemic control and lens transparency in patients with type 1 diabetes mellitus. *Am. J. Ophthalmol*. 2001; 131: 301-4.
[16] S. Kato, T. Oshika, J. Numaga *et al*. Influence of rapid glycemic control on lens opacity in patients with diabetes mellitus. *Am. J. Ophthalmol.* 2000; 130: 354-5.
[17] H. Hers. Le Mechanisme de la transformation de glucose en fructose par les vesicules seminales. *Biochim. Biophys. Acta.* 1956; 22: 202–3.
[18] H Van. Formation of polyols by the lens of the rat with 'sugar' cataract. *Nature.* 1959; 468: 194–5.
[19] J. Kinoshita. Mechanisms initiating cataract formation. *Proctor lecture Inv. Ophthalmol*. 1974; 13 (10): 713–24.
[20] J. Kinoshita, S. Fukushi, P. Kador *et al*. Aldose reductase in diabetic complications of the eye. *Metabolism.* 1979; 28 (4): 462–9.
[21] P. Kador, J. Kinoshita. Diabetic and galactosaemic cataracts. Ciba. *Foundation. Symposium*. 1984; 106: 110–31.
[22] R. Neil, J. Williamson, M. Brownlee. Hyperglycemia, Diabetes and Vascular Disease. Spriger new York (1992).
[23] P. Huang, Z. Jiang, S. Teng *et al*. Synergism between phospholipase D2 and sorbitol accumulation in diabetic cataract formation through modulation of NaK-ATPase activity and osmotic stress. *Experi. Eye Res*. 2006; 83 (4): 939–48.
[24] M. Datiles, P. Kador. Type I diabetic cataract. *Archi. Ophthalmol*. 1999; 117 (2): 284–5.
[25] Y. Kumamoto, Y. Takamura, E. Kubo *et al*. Epithelial cell density in cataractous lenses of patients with diabetes: association with erythrocyte aldose reductase. *Experi. Eye. Research*. 2007; 85 (3): 393–9.
[26] M. Mulhern, C. Madson, A. Danford *et al*. The unfolded protein response in lens epithelial cells fromgalactosemic rat lenses. *Inv. Ophthalmol. Visual. Science*. 2006; 47 (9): 3951–9.
[27] R. Elanchezhian, P. Palsamy, C. Madson *et al*. Low glucose under hypoxic conditions induces unfolded protein response and produces reactive oxygen species in lens epithelial cells. *Cell. Death. Disease*. 2012; 3: e301.
[28] K. Ornek, F. Karel, Z. Buyukbingol. May nitric oxide molecule have a role in the pathogenesis of human cataract? *Experi. Eye. Research*. 2006; 76 (1): 23–7.
[29] S. Chiou, C. Chang, C Chou *et al*. Increased nitric oxide levels in aqueous humor of diabetic patients with neovascular glaucoma. *Diab. Care*. 1999; 22 (5): 861–2.
[30] A. Stitt. The Maillard reaction in eye diseases. *Annals. New York. Acad. Sci.* 2005; 1043: 582–97.
[31] A. Behndig, K. Karlsson, A. Reaume *et al*. *In vitro* photochemical cataract in mice lacking copper-zinc superoxide dismutase. *Free. Radical. Bio. Med*. 2001; 31(6): 738–44.
[32] E. Olofsson, S. Marklund, K. Karlsson *et al*. In vitro glucose-induced cataract in copper-zinc superoxide dismutase null mice. *Exp. Eye. Res.* 2005; 81 (6): 639–46.
[33] E. Olofsson, S. Marklund, A. Behndig *et al*. Enhanced diabetes-induced cataract in copper-zinc superoxide dismutase-null mice. *Invest. Ophthalmol. Visual. Sci*. 2009; 50 (6): 2913–18.
[34] J. Lemagne, O. Kallay. Astigmatism after a large scleral pocket incision in extracapsular cataract extraction. J. Cataract. *Refractive. Surg*. 1993; 19: 613-15.
[35] A. Landen, H. Preston, R. Brian. Outcomes of manual extracapsular versus phacoemulsification cataract extraction by beginner resident surgeons. *J. Cataract. Refractive. Surg.* 2013; 39 (11): 1698–1701.
[36] J. Goldstein. How a jolt and a bolt in a dentist's chair revolutionized cataract surgery. *Nature. Med.* 2004; 10 (10): 1032–3.
[37] S. Sadiq, A. Chatterjee, S. Vernon. Progression of diabetic retinopathy and rubeotic glaucoma following cataract surgery. *Eye.* 1995; 9 (6): 728–38.
[38] P. Tranos, S. Wickremasinghe, N. Stangos *et al*. Survey. *Ophthalmol*. 2004; 49 (5): 470–490.
[39] K. Wang, C. Cheng. Central retinal thickness changes and visual outcomes following uncomplicated small-incision phacoemulsification cataract surgery in diabetic without retinopathy patients and nondiabetic patients. *Taiwan. J. Ophthalmol*. 2014; 4: 33-39.

[40] Y. Liu, L. Luo, M. He *et al*. Disorders of the blood-aqueous barrier after phacoemulsification in diabetic patients. *Eye.* 2004; 18 (9): 900–4.
[41] J. Schmier, M. Halpern, D. Covert *et al*. Evaluation of costs for cystoid macular edema among patients after cataract surgery. *Retina.* 27 (5): 621–8.
[42] S. Kim, R. Equi, M. Neil. Analysis of Macular Edema after Cataract Surgery in Patients with Diabetes Using Optical Coherence Tomography. *Ophthalmol.* 2007; 114 (5): 881–9.
[43] H. Laura, V. Lambermont, S. Jan *et al*. Prevention of Cystoid Macular Edema After Cataract Surgery in Nondiabetic and Diabetic Patients: A Systematic Review and Meta-Analysis. *Am. J. Ophthalmol.* 2015; 160 (5)**:** 968–81.
[44] D. Patel, S. Prasad, R. Kumar *et al*. Cataract: A major secondary complication of diabetes, its epidemiology and an overview on major medicinal plants screened for anticataract activity. *Asian. Pacific. J. Tropical. Disease.*2011; 1 (4): 323–29.
[45] R. Asha, V. Gayathri, A. Abraham. A pentacyclic triterpenoid isolated from *Vernonia cinerea* attenuate selenite induced cataract formation in Sprague Dawley rat pups. *Chemico-Biological. Interactions*. 2016; 245**:** 20–29.
[46] P. Munipally, S. Venui, R. Naik *et al*. The inhibitory effect of Isoflavones isolated from *Caesalpinia pulcherrima* on aldose reductase in STZ induced diabetic rats. *Chemico-Biological. Interactions*. 2015; 237**:** 18–24.
[47] Y. Miyata, T. Oshitari, Y. Okuyama *et al*. Polymethoxyflavones as agents that prevent formation of cataract: Nobiletin congeners show potent growth inhibitory effects in human lens epithelial cells. *Bio-organic. Medicinal. Chem. Letters*. 2013; 23 (1): 183–87.
[48] J. Kim. Chapter 45 – Seeds of *Cornus officinalis* and Diabetic Cataracts. *Handbook of Nutrition, Diet and the Eye.* 2014; 451–8.
[49] M. Onkaramurthy, V.P. Veerapur, B.S. Thippeswamy *et al*. Anti-diabetic and anti-cataract effects of *Chromolaena odorata* Linn., in streptozotocin-induced diabetic rats. *J. Ethnopharmacol.* 2013; 145 (1): 363–72.
[50] V. Dongare, C. Kulkarni, M. Kondawar *et al*. Inhibition of aldose reductase and anti-cataract action of trans-anethole isolated from *Foeniculum vulgare* Mill. Fruits. *Food Chemistry*. 2012; 132: 385–390.
[51] V. Vats, S. Yadav, N. Biswas *et al*. Anti-cataract activity of Pterocarpus marsupium bark and *Trigonella foenum-graecum* seeds extract in alloxan diabetic rats. *J. Ethnopharmacol.* 2004; 93: 289–94.
[52] M. Moghaddam, P. Kumar, G. Reddy *et al*. Effect of Diabecon on sugar-induced lens opacity in organ culture: mechanism of action. *J. Ethnopharmacol*. 2005; 97 (2): 397–403.
[53] N. Halder, S. Joshi, S. K. Gupta. Lens aldose reductase inhibiting potential of some indigenous plants. *J. Ethnopharmacol*. 86 (1): 113–6.
[54] M. Jacobson, Y. Sharma, E. Cotlier *et al*. Diabetic complications in lens and nerve and their prevention by sulindac or sorbinil: two novel aldose reductase inhibitors. *Invest. Ophthalmol. Visual. Sci*. 1983; 24 (10): 1426–29.
[55] Y. Sharma, R. Vajpayee, R. Bhatnagar, *et al*. Topical sulindac therapy in diabetic senile cataracts: cataract—IV. Ind. *J. Ophthalmol.* 1989; 37 (3): 127–33.
[56] S. Gupta, S. Joshi. Relationship between aldose reductase inhibiting activity and anti-cataract action of various non-steroidal anti-inflammatory drugs. *Dev. Ophthalmol*. 1991; 21: 151–6.
[57] S. Gupta, S. Joshi. Naproxen: an aldose reductase inhibitor and potential anti-cataract agent. *Dev. Ophthalmol*. 1991; 21: 170–8.
[58] E. Cotlier. Aspirin effect on cataract formation in patients with rheumatoid arthritis alone or combined to diabetes. *Intern. Ophthalmol.* 1981; 3 (3): 173–7.
[59] A. Pollreisz, U. Erfurth. Diabetic Cataract—Pathogenesis, Epidemiology and Treatment. *J. Ophthalmol*. 2010; 1-8.
[60] L. Yun, L. Ya-Zhen, S. Jing-Ming *et al*. Alpha lipoic acid protects lens from H_2O_2-induced cataract by inhibiting apoptosis of lens epithelial cells and inducing activation of anti-oxidative enzymes. *Asian Pac. J. Trop. Med*. 2013; 6(7): 548–51.
[61] I. Maitra, E. Serbinova, H. Trischler *et al*. α-lipoic acid prevents buthionine sulfoximine-induced cataract formation in newborn rats. *Free Radical Biology and Medicine*. 1995; 18 (4): 823–9.
[62] M. Yoshida, H. Kimura, K. Kyuki *et al*. Combined effect of vitamin E and insulin on cataracts of diabetic rats fed a high cholesterol diet. *Biol. Pharm. Bulletin*. 2004; 27 (3): 338–44.
[63] J. McNeil, L. Robman, G. Tikellis *et al*. Vitamin E supplementation and cataract: randomized controlled trial. *Ophthalmol.* 2004; 111(1): 75-84.
[64] W. Zhao, P. Devamanoharan, M. Henein *et al*. Diabetes-induced biochemical changes in rat lens: attenuation of cataractogenesis by pyruvate. *Diabetes, Obesity and Metabol*. 2000; 2 (3): 165–74.