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# THE EFFECTIVENESS OF THERAPEUTIC AGENTS IN THE TREATMENT OF AGE-RELATED CATARACT: A SYSTEMATIC REVIEW.

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## Abstract

**Context:** The effectiveness of therapeutic agents in the treatment of age-related cataract has been studied by many authorities and nothing concrete has been documented to encourage further discourse on follow-ups and pharmaceutical trials.

**Objective:** To investigate the effectiveness of therapeutic agents in the treatment of age-related cataract.

**Data Sources:** The search engines employed include PUBMED and EBSCO research Databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, E-journals and Open Dissertations).

**Study Selection:** The key words used were "age-related cataract", "drug treatment", "cataract" and "pharmacotherapy". There was no language restriction. Studies were random controlled trials and quasi experiments that reported relative risks, odds ratios or hazard ratios with 95%CI for their reported results.

**Data Extraction:** Independent mining of articles by one author applying already defined data fields, including study value pointers.

**Data Synthesis:** Data was put on a spread sheet and analyzed according to the study parameters of interest.

**Results:** 90 percent of the studies reported a measure of effects on age-related cataracts in humans and enucleated cataractous human lens nuclei, horses, dogs, and goats, and induced cataracts in rats and rabbits.

**Conclusions:** Many substances have been researched and shown to inhibit development and progression of age-related cataract in human eyes and in selenite and diabetic cataracts in animal models. It is possible to ameliorate cataract with pharmacotherapy once the right combination of agents is discovered.

**Keywords:** Age-related cataract, pharmacotherapy, cataract, drug treatment.

## Introduction

Cataract is the opacification of the crystalline lens in the eye leading to loss of vision when light is either scattered or absorbed, resulting in compromised or reduced visual acuity. It is the second leading cause of blindness globally and the leading cause of blindness and moderate to severe visual impairment in developing and underdeveloped regions where surgical intervention is limited.[1] Age-related cataract

1. Gupta VB, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: an appraisal. Ind J Ophthalmol 2014;62(2):103-110. doi:10.4103/0301-4738.121141.

is the major type of cataract encountered in both developed and underdeveloped regions. It constitutes a major public health burden and the problem is expected to increase as more people age.

A cataract is formed when the transparent crystalline lens becomes cloudy and loses its transparency. The medium begins to scatter light and there is corresponding decrease in visual acuity and glare sensation. It is reported that the crystallin proteins in the lens are broken down and aggregate; there is damage to the cell fiber membranes; deficiency of glutathione; abnormal migration of lens epithelial cells and a number of other disruptions in the lens metabolism.[1,2] Differentiated epithelial cells migrate to the center of the lens and stretch to form sheets of fiber within the cortex and nucleus producing crystallin proteins. These proteins are the major components of the lenticular protein matter. But after differentiation they become inactive and lose their functionality.[3]

The only widely accepted treatment for cataract is surgery (phacoemulsification and extracapsular cataract extraction) and no drug therapy has been creditably acknowledged as an alternative to surgical removal and replacement of the crystalline lens.

Cataracts typically affect people in their twilight and some may start a bit earlier. The causes of cataracts have been narrowed down principally to age and also to include the presence of diabetes mellitus,[4] use of corticosteroids and other drugs,[5] smoking,[6,7] alcohol,[8,9] nutritional deficiencies[10] and ultraviolet radiation.[11,12,13] in addition to others. Many studies have shown that cortical cataracts are mainly caused by exposure to atmospheric ultraviolet rays in addition to ageing.[14,15,16]

In the search for therapeutic alternatives to cataract resolution, many studies have employed human cataracts in longitudinal studies and others have used extracted lens nuclei for in vitro experiments. Many studies on animal models have induced cataracts in rats, rabbits, chicks and bovine/equine subjects. No studies in induced cataracts in animals can adequately mimic the age-related cataractogenesis found in humans especially as a result of the time it takes for age-related cataract to form in humans.

A combination of UV exposure, genetic manipulation, xenobiotics (chemical substances foreign to animals), calcium, hydrogen peroxide and high sugar induction have been employed by many researchers in the quest for in vivo cataract models.[17]

1. Gupta VB, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: an appraisal. Ind J Ophthalmol 2014;62(2):103-110. doi:10.4103/0301-4738.121141.
2. Moreau KL, King JA. Protein misfolding and aggregation in cataract disease and prospects for prevention. Trends Mol Med 2012;18(5):273-82. doi: 10.1016/j.molmed.2012.03.005.
3. Lian RR, Afshari NA. The quest for homeopathic and nonsurgical cataract treatment. Curr Opin Ophthalmol 2020;31:61–66. doi:10.1097/ICU.0000000000000631.
4. Cumming RG, Mitchell P. Medications and cataract. The Blue Mountains Eye Study. Ophthalmol 1998;105(9):1751-8.
5. Robman L, Taylor H. External factors in the development of cataract. Eye 2005;19(10):1074-82.
6. Chang JR, Koo E, Agrón E, et al. Risk factors associated with incident cataracts and cataract surgery in the Age Related Eye Disease Study (AREDS). AREDS Report Number 32. Ophthalmol 2011;118(11):2113–2119.
7 Gong Y, Feng K, Yan N, Xu Y, Pan C. Different Amounts of Alcohol Consumption and Cataract: A Meta-Analysis. Optom Vis Sci 2015;92(4):471-9.
8 Hiratsuka Y, Ono K, Murakami A. Alcohol use and cataract. Curr Drug Abuse Rev 2009;2(3):226-9.
9 Tan AG, Mitchell P, Flood VM, et al. Antioxidant nutrient intake and the long-term incidence of age-related cataract: the Blue Mountains Eye Study. Am J Clin Nutr 2008;87:1899–905.
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14 Taylor HR. Ultraviolet radiation and the eye: an epidemiologic study. Trans Am Ophthalmol Soc, 1989;87:802–853.
15 Graziosi P, Rosmini F, Bonacini M, et al. Location and severity of cortical opacities in different regions of the lens in age-related cataract. Ophthalmol Vis Sci. 1996;37:1698-1703.
16 Sasaki H, Kawakami Y, Ono M, et al. Localization of Cortical Cataract in Subjects of Diverse Races and Latitude. Invest Ophthalmol Vis Sci. 2003;44:4210–4214.
17 Harding J. Experimental opacification of the lens in vivo and in vitro. In: Harding J, ed. Cataract: Biochemistry, Epidemiology and Pharmacology. London: Chapman and Hall, 1991:125–194.

## METHODOLOGY

### Search strategy and Selection Criteria

The primary objective of this review was to evaluate primary research works that have been done on non-surgical interventions of age-related cataract. Most of the works evaluated were conducted in vivo in animal models and some were done in vitro in animal models. Others were conducted in vivo in human subjects and yet others were conducted in enucleated lens nuclei. Studies were done between January 2008 and October 2022. Literature reviews and systematic reviews were excluded from the study. There was neither language restriction in the search for review articles nor restrictions in human versus animal studies. Studies used were cohort studies, random controlled trials and quasi-experiments that reported relative risks, odds ratios or hazard ratios with 95% CI for their reported results. The key words used were "age-related cataract", "drug treatment", "cataract" and "pharmacotherapy".

**Table 1. Selection Criteria**

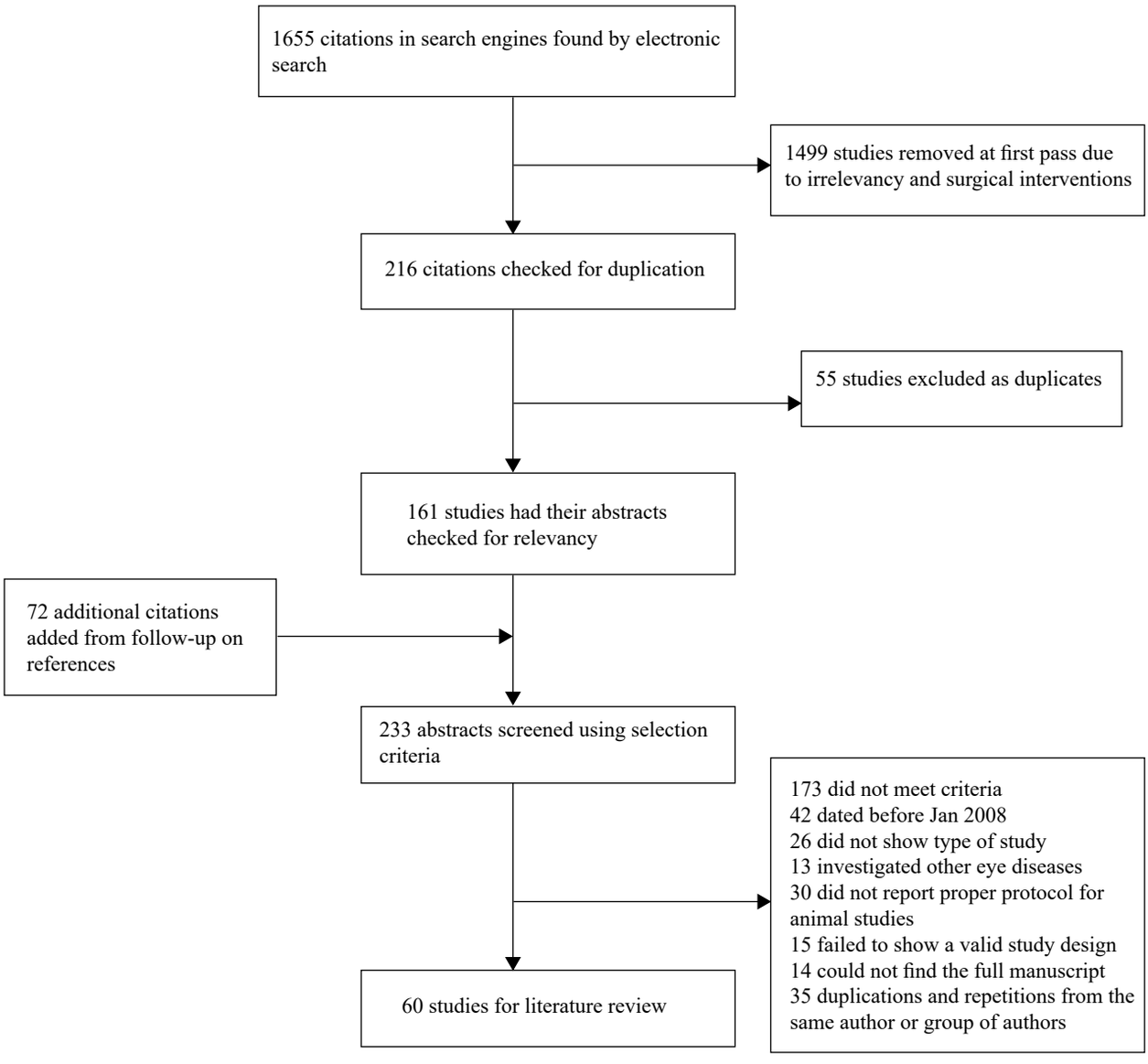
| SELECTION CRITERIA | INCLUSION CRITERIA | EXCLUSION CRITERIA |
|---|---|---|
| Date of publication between January 2008 and October 2022 | Studies conducted between January 2008 and October 2022 | Studies conducted before January 2008 |
| | | Studies conducted with more than one objective other than cataract in animal models |
| | | Literature reviews and systematic reviews |
| Studies published in peer-reviewed journals | Intervention studies based on random controlled studies or quasi-experimental design with comparison or control groups | Studies reporting cataract in younger people under 45 years of age |
| Studies providing original data on clinical questions | | |

The search engines employed include PUBMED and EBSCO research Databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, E-journals and Open Dissertations).

The first search with all the parameters fully plotted yielded 1,665 studies. At first inspection, 1,449 studies were immediately discarded because they were outside the subject matter or dealt with surgical interventions. The 216 remaining studies were checked for duplication and the number was further reduced to 161. During the course of the review, some references were followed up and another 72 related studies were added to the number and these 233 studies were screened from their abstracts into included and excluded studies using the already established inclusion and exclusion

criteria as listed in Table 1.

173 studies failed to meet the inclusion criteria for the systematic review. 42 studies were dated before January 2008. 26 studies did not show type of study or proper description of methods. 13 studies investigated other eye diseases and only gave corollary reports about cataract. 30 other studies did not report proper protocol for animal studies and methods of induction with xenobiotics or euthanization. 15 studies did not report a valid study design with hazard ratios, odds ratios or risk ratios. The author could not access the full manuscript of 14 studies even though the abstracts were available and so they were discarded. The last 35 studies were duplications and repetitions from the same author or group of authors.



## RESULTS

### Table 2

Table showing the studies evaluated with citations, subjects, study design, mode of induction of cataract, independent variable (agent used) and results

| S/N | Study | Subject | n | Study design | Mode of induction | Independent variable | Remarks |
|---|---|---|---|---|---|---|---|
| 1. | Age-Related Eye Disease Study Research Group[18] | Humans | 4757 | RCT | ARC | Vitamin E & C | No effect |
| 2. | Abdel-Ghaffar A *et al*[36] | Rats | | Laboratory experiment | Fructose/ Streptozotocin | Ursodeoxycholic acid | UDCA decreased incidence of diabetic cataract |
| 3. | Age-Related Eye Disease Study 2 Research Group, Chew EY et al.[71] | Humans | 4203 | RCT | ARC | Lutein/ zeaxanthin | No effect |
| 4. | Agarwal R *et al*.[37] | Sprague-Dawley rats | 45 | Laboratory experiment | Galactose | Magnesium taurate | Magnesium taurate reduced onset of cataract |
| 5. | Asha R *et al*.[39] | Sprague-Dawley rats | 24 | Laboratory experiment | Selenite | Lupeol from *Vernonia cinerea* | Lupeol had effect on cataract by scavenging free radicals |
| 6. | Abdul Nasir NA *et al*[40] | Sprague-Dawley rats | 72 | Laboratory experiment | Galactose | Tocotrienol | Less than 0.05 – 0.01% delay in onset and progression of cataracts |
| 7. | Akiyama N, et al[41] | Rats | | Laboratory experiment | Glucorcorticoid Diamide Galactose | N-beta-alanyl-5-S-glutathionyl-3,4-dihydroxyphenylalanine (5-S-GAD) | 5-S-GAD prevents opacification in short term experimental models |
| 8. | Atalay HT et al[43] | Wistar Rats | 26 | Laboratory experiment | Selenite | Sildenafil | Low dose Sildenafil (0.7mg/ kg) reduces oxidative stress and shows less cataract maturity than in the other groups |

18 Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol. 2001;119(10):1439-1452. doi:10.1001/archopht.119.10.1439

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37 Agarwal R, Lezhitsa L, Awaludin NA, et al.Effects of magnesium taurate on the onset and progression of galactose-induced experimental cataract: in vivo and in vitro evaluation. Exp Eye Res 2013;110:35-43. doi: 10.1016/j.exer.2013.02.011.

39 Asha R, Gayathri Devi V, Abraham A. Lupeol, a pentacyclic triterpenoid isolated from Vernonia cinerea attenuate selenite induced cataract formation in Sprague Dawley rat pups. Chem Biol Interact. 2016;245:20-29.

40 Abdul Nasir NA, Agarwal R, Vasudevan S, et al. Effects of topically applied tocotrienol on cataractogenesis and lens redox status in galactosemic rats. Mol Vis. 2014;20:822-835.
PMID: 24940038; PMCID: PMC4057512.

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43 Atalay HT, Ucgul AY, Turkcu UO, Ozmen MC, Yilmaz S, Bilgihan A. The Effect of Sildenafil on Selenite-Induced Cataract in Rats. Curr Eye Res. 2020;45(9):1082-1088. doi: 10.1080/02713683.2020.1726405. Epub 2020 Feb 11. PMID: 32023416.

71 Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, San Giovanni JP, et al. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. JAMA Ophthalmol. 2013;131(7):843-850. doi:10.1001/jamaophthalmol.2013.4412.

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| 9. | Babizhayev MA *et al*[25] | Humans | 147 | Random, double-blind clinical cohort study | ARC | N-acetylcarnosine | N-acetylcarnosine eye drops helped the aging eye to improve clarity, glare sensitivity, color perception and overall vision |
| 10. | Cao J *et al*[29] | Wistar Rats | 18 | Laboratory experiment | Selenite | Curcumin | Curcumin inhibited selenite-induced cataract by bringing down the intra cellular production of ROS and defense from oxidation. P<0.05 |
| 11. | Chemerovski-Glikman M *et al*[28] | Enucleated human les | 80 | Experimental ex vivo in human lens nuclei. | ARC | Rosmarinic acid | Treatment with Rosmarinic acid cause 90% reduction of cataract turbidity (n=14, P = 0.001) |
| 12. | Christen WG *et al*[19] | Humans (Men) | 35,533 | RCT | ARC | Selenium Vitamin E | No effect |
| 13. | Grama CN *et al*[30] | WNIN Rats | 31 | Laboratory experiment | Galactose | Curcumin Nanocurcumin | Significant delay in the onset and progression of cataract in the nanocurcumin group P < 0.001 (P = -0.298, SE = 0.091 |
| 14. | Fang W *et al*[44] | Sprague-Dawley rats | | Laboratory experiment | Selenite | Trimetazidine | Trimetazidine could put a stop to the maturation of sodium selenite-induced cataract in a rat model |
| 15. | Zhang R *et al*[45] | Rats | 40 | Laboratory experiment | Selenite | Idelalisib | Idelalisib could successfully slow down lens oxidative pressure and apoptosis |
| 16. | Avetisov SE *et al*[72] | Rats | | Laboratory experiment | Ultraviolet light | N-acetyl carnosine + D-patethine | Combined preparation has a protective effect on rat lens tissue |

19 Christen WG, Glynn RJ, Gaziano JM, et al. Age-related cataract in men in the selenium and vitamin E cancer prevention trial eye endpoints study: a randomized clinical trial. JAMA Ophthalmol. 2015;133(1):17-24.
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29 Cao J, Wang T, Wang M. Investigation of the anti-cataractogenic mechanisms of curcumin through in vivo and in vitro studies. BMC Ophthalmol. 2018;18(1):48.
30 Grama CN, Suryanarayana P, Patil MA, et al. Efficacy of biodegradable curcumin nanoparticles in delaying cataract in diabetic rat model. PLoS One. 2013;8(10):e78217.
44 Fang W, Ye Q, Yao Y, Xiu Y, Gu F, Zhu Y. Protective Effects of Trimetazidine in Retarding Selenite-Induced Lens Opacification. Curr Eye Res. 2019;44(12):1325-1336. doi: 10.1080/02713683.2019.1633359.
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72 Avetisov SE, Polunin GS, Sheremet NL, et al. Vestn Oftalmol. 2008;124(2):12-16.

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| 17. | Avetisov SÉ *et al*[73] | Rats | | Laboratory experiment | UV-A light | N-acetyl carnosine + D-patethine | Combined preparation reduced effects on rats lens |
| 18. | Babizhayev MA *et al*[24] | Humans | 50,500 | prospective, randomized, double-masked, placebo-controlled crossover clinical trial | ARC | N-acetyl carnosine | N-acetyl carnosine promotes healthy vision and prevent vision disability from senile cataracts |
| 19. | Christen WG *et al*[26] | Humans (men) | 14,641 | Randomized, double-blind, placebo-controlled trial | ARC | Multivitamin supplementation | Long-term daily multivitamin use modestly and significantly decreased the risk of cataract |
| 20. | Daszynski DM *et al*[20] | Sprague-Dawley Rats | 24 | Laboratory experiment | -Blunt trauma -Ouabain -Toxic glycoprotein | Oxysterols (lanosterol, 25-hydroxycho-lesterol) | oxysterols have no anti-cataractogenic activity on osmotic lens cataract |
| 21. | Zhang K *et al*[74] | Cynomolgus monkeys | 9 | Laboratory experiment | ARC | Lanosterol | Lanosterol showed a short-term and reliable reversal effect on reducing cataract severity in cortical cataract |
| 22. | De Bruyne S *et al*[68] | Horses | 6 | Laboratory experiment | ARC | Fructosamine-3-Kinase | FN3K treatment, color restoration could be observed within 30 min |
| 23. | Demir E *et al*[46] | Sprague-Dawley rats | 74 | Laboratory experiment | Ionizing radiation | Nigella sativa oil (NSO), thymoquine, propolis, or caffeic acid phenethyl ester (CAPE) | NSO and propolis could prevent cataractogenesis in radiation induced cataracts in mice |
| 24. | Dubey S *et al*[63] | Goat | 42 | Laboratory experiment | Hydrogen peroxide | Seabuckthorn (SBT) leaf extract | SBT leaves showed the potential to delay onset and/ or progression of cataract, at least during in vitro conditions |

20 Daszynski DM, Santhoshkumar P, Phadte AS, et al. Failure of Oxysterols Such as Lanosterol to Restore Lens Clarity from Cataracts. Sci Rep 2019;9(1). doi:10.1038/s41598-019-44676-4.
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63 Dubey S, Deep P, Singh AK. Phytochemical characterization and evaluation of anticataract potential of seabuckthorn leaf extract. Vet Ophthalmol. 2016;19(2):144-148. doi:10.1111/vop.12271.
68 De Bruyne S, van Schie L, Himpe J, et al. A Potential Role for Fructosamine-3-Kinase in Cataract Treatment. Int J Mol Sci. 2021;22(8):3841. doi:10.3390/ijms22083841.
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| 25. | Dubey S *et al*[64] | Goat | | Laboratory experiment | Hydrogen peroxide | Abies pindrow leaf extract (APE) | APE can delay the onset and/ or prevent the progression of cataract |
| 26. | Gajjar D *et al*[70] | Human lens epithelial cells | | Laboratory experiment | Hydrogen peroxide | Oestradiol | Oestradiol hindered catalase production within 5 minutes |
| 27. | Jablecka A *et al*[34] | Rabbits | No data | Laboratory experiment | Alloxan | Angiotensin-converting enzyme (ACE) inhibitors Enelapril Captopril | Six-month administration of ACEI to rabbits resulted in a delay of diabetic cataractogenesis |
| 28. | Kawada H *et al*[42] | Brown Norway rats | 32 | Laboratory experiment | UV-B | 5-S-GAD | 5-S-GAD eyedrop application may delay the progression of UV-B-induced cataract in rats. |
| 29. | Kumari RP *et al*[47] | Wistar rats | 24 | Laboratory experiment | Selenite | C-Phycocyanin (C-PC) | C-PC treatment possibly prevented cataractogenesis |
| 30. | Li W *et al*[48] | Male albino rats | No data | Laboratory experiment | Streptozotocin | Glycine Sorbinin | Glycine supplementation resulted in reduction of glucose and delayed the development of diabetic cataracts. |
| 31. | Liao JH *et al*[49] | Rats | No data | Laboratory experiment | UV-C | Ferulic acid, Cinnamic acid, Vanillin, Vanillic acid | Ferulic acid exhibited a significant inhibitory effect against UVB-induced turbidity |
| 32. | Makri OE *et al*[54] | Wistar rats | 26 | Laboratory experiment | Selenite | *Crocus sativus* stigmas (saffron) extract | Saffron extract hindered selenite-induced cataract formation |

34 Jablecka A, Czaplicka E, Olszewski J, Bogdanski P, Krauss H, Smolarek I. Influence of selected angiotensin-converting enzyme inhibitors on alloxan-induced diabetic cataract in rabbits. Med Sci Monit. 2009;15(11):BR334-BR338.
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49 Liao JH, Huang YS, Lin YC, Huang FY, Wu SH, Wu TH. Anticataractogenesis Mechanisms of Curcumin and a Comparison of Its Degradation Products: An in Vitro Study. *J Agric Food Chem.* 2016;64(10):2080-2086. doi:10.1021/acs.jafc.6b00430.
54 Makri OE, Ferlemi AV, Lamari FN, Georgakopoulos CD. Saffron administration prevents selenite-induced cataractogenesis. *Mol Vis*. 2013;19:1188-1197.
64 Dubey S, Saha S, Saraf SA. In vitro anti-cataract evaluation of standardised Abies pindrow leaf extract using isolated goat lenses. *Nat Prod Res*. 2015;29(12):1145-1148. doi:10.1080/14786419.2014.980250.
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| 33. | Mani Satyam S *et al*[59] | Wistar rats | No data | Laboratory experiment | Selenite | Grape seed extract<br>Zinc | Combined formulation of grape seed extract and Zinc tablets may offer a prophylactic measure against onset and progression of age-related cataract |
| 34. | Manikandan R *et al*[31] | Rats | No data | Laboratory experiment | Selenite | Curcumin | Curcumin has the potential to function as an anticataractogenic agent, possibly by preventing free radical-mediated accumulation of Ca(2+) in the eye lens. |
| 35. | Clinical Trial of Nutritional Supplements and Age-Related Cataract Study Group, Maraini G *et al*[21] | Humans | 1020 | Randomized, double-masked, placebo-controlled clinical trial | ARC | Multivitamin supplementation | No effect |
| 36. | Milton RC *et al*[27] | Humans | 4590 | Clinic-based prospective cohort study. | ARC | Centrum (multivitamins) | Use of a multivitamin may delay the progression of lens opacities. |
| 37. | Nakazawa Y *et al*[50] | Sprague-Dawley rats | No data | Laboratory experiment | Selenite | α glucosyl hesperidin | Oral intake of α glucosyl hesperidin could impede the onset of selenite induced cataract |
| 38. | Park S *et al*[23] | Dogs | 172 | Retrospective study | ARC | Antioxidants | There was no significant delaying effect of oral antioxidants on incipient cataract progression but antioxidants could be used to delay the progression of senile immature cataract. |

21 Clinical Trial of Nutritional Supplements and Age-Related Cataract Study Group, Maraini G, Williams SL, et al. A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities. Clinical trial of nutritional supplements and age-related cataract report no. 3. Ophthalmology 2008;115(4):599-607.e1. doi:10.1016/j.ophtha.2008.01.005

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59 Mani Satyam S, Kurady Bairy L, Pirasanthan R, Lalit Vaishnav R. Grape seed extract and zinc containing nutritional food supplement prevents onset and progression of age-related cataract in wistar rats. J Nutr Health Aging. 2014;18(5):524-530. doi:10.1007/s12603-014-0020-8.

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| 39. | Patil KK *et al*[57] | Goats | 6 | Laboratory experiment | Glucose | Monohydroxylated flavonoids | 7-hydroxy flavonoid is a possible anti-glycating and anti-cataract agent |
| 40. | Randazzo J *et al*[33] | 1. Male Long Evans rats 2. Sprague-Dawley rats | 24 | Laboratory experiment | 1. Gamma irradiation 2. Streptozotocin | Multifunctional antioxidants | Multi-functional antioxidants inhibited cataract formation in gamma-irradiated and streptoztocin induced rat models |
| 41. | Sadik NAH *et al*[51] | Rats | 40 | Laboratory experiment | Galactose | Esculentin Idebenone | Esculetin and Idebenone have anticataractogenic potentials due to their antioxidant and antiapoptotic properties. |
| 42. | Shanmugam PM *et al*[22] | Cataractous human lens nuclei | 40 | Laboratory experiment | ARC | Lanosterol | No effect |
| 43. | Shi Q *et al*[75] | Sprague-Dawley rats | 120 | Laboratory experiment | Streptozotocin | Carnosine Aspirin Carnosine + aspirin | Carnosine + aspirin are effective against the onset and development of diabetic cataract in rats |
| 44. | Shree J *et al*[35] | Sprague-Dawley rats | 30 | Laboratory experiment | Streptozotocin | Angiotensin modulators (Aliskiren Enalapril, Olmesartan Angiotensin 1-7) | Topical treatment with renin angiotensin modulators delayed the onset of diabetes-induced cataract formation. |
| 45. | Soni P *et al*[53] | Sprague-Dawley albino rats | No data | Laboratory experiment | Fructose | *Coleus forskohlii* leaf-extract | C. forskohlii led to significant restoration of lens antioxidants enzyme level and reduced cataract formation in rats |
| 46. | Soni P *et al*[56] | Goat lens (in vitro) Rats lens (in vivo) | 30 | Laboratory experiment | Fructose | *Alstonia scholaris* | Administration of Alstonia scholaris played a vital role in the decline of cataract formation in diabetic and hypertensive models. |

22 Shanmugam PM, Barigali A, Kadaskar J, et al. Effect of lanosterol on human cataract nucleus. Indian J Ophthalmol. 2015;63(12):888-890. doi:10.4103/0301-4738.176040.
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| 47. | Sreelakshmi V *et al*[58] | Sprague-Dawley rats | No data | Laboratory experiment | Selenite | Cassia tora | C. tora might prevent lens opacity |
| 48. | Tang CF *et al*[69] | Wistar rats | No data | Laboratory experiment | Selenite | Dajizhi (Euphorbium) eye drops | Euphorbium may help lenses fight oxidative stress caused by selenite. |
| 49. | Thiagarajan R *et al*[76] | Male albino Wistar rats | No data | Laboratory experiment | Selenite | Vitamin K1 | Vitamin K1 is a potent inhibitor of lens aldose reductase enzyme |
| 50. | Thiraphatthanavong P *et al*[60] | Male Wistar rats | No data | Laboratory experiment | Glucose | Zea Mays L. | Purple waxy corn seeds extract is a possible contender for protection against diabetic cataract |
| 51. | Tsai CF *et al*[32] | Sprague-Dawley rats | 50 | Laboratory experiment | Selenite | Rosmarinic acid | Rosmarinic acid is a possible anti-cataract agent that probably delays the onset and progression of cataracts induced by sodium selenite. |
| 52. | Umran NSS *et al*[55] | Rats | No data | Laboratory experiment | Strepeozotocin | Citrus hystrix leaf extract (CLE) | The CLE indicated cataract healing properties |
| 53. | Varma SD *et al*[52] | Sprague-Dawley rats | No data | Laboratory experiment | Galactose | Caffeine | Caffeine eye drops was found to significantly inhibit the onset as well as the progress of cataract formation |
| 54. | Velpandian T *et al*[65] | Chick embryo Rats Rabbits | No data | Laboratory experiment | Selenite Galactose | Calcium dobesilate (CDO) | CDO showed significant defense against cataract in experimental models |
| 55. | Wattanathorn J *et al*[61] | Male Wistar rats | No data | Laboratory experiment | Streptozotocin | Mangifera indica L (Mango) Polygonum odoratum L. (Vietnamese coriander) (MPO) | MPO is the possible candidate to protect against diabetic cataract |

32 Tsai CF, Wu JY, Hsu YW. Protective Effects of Rosmarinic Acid against Selenite-Induced Cataract and Oxidative Damage in Rats. *Int J Med Sci.* 2019;16(5):729-740. Published 2019 May 10. doi:10.7150/ijms.32222.
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76 Thiagarajan R, Varsha MKNS, Srinivasan V, Ravichandran R, Saraboji K. Vitamin K1 prevents diabetic cataract by inhibiting lens aldose reductase 2 (ALR2) activity. Sci Rep. 2019;9(1):14684. doi:10.1038/s41598-019-51059-2.

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| 56. | Yang CX *et al*[66] | Sprague-Dawley rats | 60 | Laboratory experiment | Selenite | Hydrogen saline | Hydrogen saline can avert selenite-induced cataract in rats. |
| 57. | Zhang M *et al*[67] | Rats | 60 | Laboratory experiment | Galactose | Ethylenediamine tetraacetic acid (EDTA) Methyl sulfonyl methane (MSM) | EDTA-MSM significantly reduced lens opacification by about 40-50% |
| 58. | Zhang X *et al*[62] | Sprague-Dawley rats | 80 | Laboratory experiment | Selenite | Grape seed proanthocyanidin extract (GSPE) | GSPE noticeably prevented selenite-induced cataract formation |
| 59. | Zhu X *et al*[77] | Female Sprague-Dawley rats | 27 | Laboratory experiment | Naphthalene | Selenium supplementation | Selenium supplementation could slow the development of naphthalene cataract |
| 60. | Choudhary R *et al*[38] | Sprague-Dawley rats | 30 | Laboratory experiment | Cadmium chloride | Magnesium taurate | MgT may be used to manage hypertensive cataractogenesis |

Sixty studies that met the inclusion criteria were evaluated after obtaining their full manuscripts and the results showed that 48 different agents and combinations of agents were used to test for pharmacotherapy of cataracts in humans, rats, rabbits, horses, monkeys, goats and dogs.

8 studies tested in humans with age-related cataracts in longitudinal studies and two studies tested some agents on enucleated human lens nuclei. One study conducted tests in human lens epithelium in the laboratory.

42 studies were conducted on rats, especially Sprague-Dawley rats and wistar rats. Cataract in these models was induced mostly by the use of selenite in 18 studies. Streptozotocin, fructose, galactose, glucose and alloxan were used to induce diabetic cataract in another 18 studies. Four studies induced cataracts in goats, rats and human epithelial cells with hydrogen peroxide and three studies achieved cataractogenesis with ultraviolet radiation. The methods/agents that were used in the remaining studies to induce cataract were gamma irradiation, ionizing radiation, cadmium chloride, naphthalene, diamide and osmosis.

Three studies were conducted on goat's eyes

38 Choudhary R, Bodakhe SH. Magnesium taurate prevents cataractogenesis via restoration of lenticular oxidative damage and ATPase function in cadmium chloride-induced hypertensive experimental animals. Biomed Pharmacother doi:10.1016/j.biopha.2016.10.012.
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77 Zhu X, Lu Y. Selenium supplementation can slow the development of naphthalene cataract. Curr Eye Res. 2012;37(3):163-169. doi:10.3109/02713683.2011.639123.

injected with hydrogen peroxide in vivo, two on rabbits and one study each on cynomolgus monkeys, horses and dogs with age-related cataracts.

Out of the sixty selected studies only six (10%) reported no effect on cataractogenesis with the pharmacotherapy employed.[18-22] The agents used in these studies were Selenium/ Vitamin E, Vitamin C & E, Multivitamins and Lanosterol/25-hydroxycholesterol. Five of the studies were on humans with age-related cataract. One study tested Lanosterol on osmosis-induced cataractous rat lens and found no effect.[20]

Fifty four studies (90%) reported a measure of effects on age-related cataracts in humans and enucleated cataractous human lens nuclei, horses, dogs and goats, and induced cataracts in rats and rabbits. These effects ranged from delay in cataractogenesis, reduction of oxidative stress, reduction in lens turbidity, and reduction of reactive oxygen species (ROS), restoration of color and improvement in vision and clarity. One study reported no effect on incipient cataract but demonstrated delay in immature senile cataract in dogs.[23]

Four of the studies that showed positive effect of pharmacotherapy on cataract were on humans with age-related cataract using multivitamin supplementation and N-acetylcarnosine.[24-27] Another study was on enucleated cataractous human lens nuclei using rosmarinic acid.[28] The remaining 49 studies that reported a level of anti-cataractogenic properties were on animal models.

The agents that showed positive effects in the remaining studies include curcumin[29-31], rosmarinic acid[28,32,] antioxidants[23,33], angiotensin-converting enzyme/angiotensin modulators (enalapril)[34,35], urseodeoxycholic acid[36] and magnesium taurate[37,38]. Others are Lupeol[39],

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21 Clinical Trial of Nutritional Supplements and Age-Related Cataract Study Group, Maraini G, Williams SL, et al. A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities. Clinical trial of nutritional supplements and age-related cataract report no. 3. Ophthalmology 2008;115(4):599-607.e1. doi:10.1016/j.ophtha.2008.01.005
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tocotrienol[40], 5-S-Glutathionyl-N-β-alanyl-3,4-dihydroxyphenylalanine (5-S-GAD)[41,42], sildenafil[43], trimetazidine[44], idelalib[45] and Nigella sativa oil (NSO)/Propolis[46]. In addition to these, C-Phycocyanin (C-PC)[47], glycine/sorbinil[48], ferulic acid[49], α-glucosyl-hesperidin[50], esculentin/idebenone[51] and caffeine[52] also demonstrated potentials as possible anti-cataractogenic agents. Some leaf/bark extracts and natural fruits were used in other studies and these include Coleus forskohlii leaf extract[53], Crocus sativus stigmas (saffron) extract[54], Citrus histrix leaf extract[55], isoflavonoid from bark of Alstonia scholaris[56], 7-hydroxyflavonoid[57], polyphenols from Cassia tora leaves[58], grape seed extract & Zinc[59], Zea mays L. (purple waxy corn)[60], Mandifera indica (Mango)/Polygonium odoratum L. (Vietnamese coriander)[61], grape seed proanthocyanidin extract (GSPE)[62], seabuckthorn (SBT) leaf extract[63] and Albies Pindrow leaf extract (APE)[64]. The remaining agents employed in the studies evaluated that showed positive interactions with induced cataracts in animal models include calcium dobesilate[65], hydrogen saline[66], ethylenediamine tetra acetic acid (EDTA)67/methyl sulphonyl methane (MSM)[67], fructosamine 3-kinase (FN3K)[68], Dajizhi (euphorbium) drops[69] and oestradiol[70].

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## DISCUSSION

Given that a lot of substances have different mechanisms for ameliorating lens opacity and progression of cataracts in human and animal models, the right combination will be a valuable key in the formulation of a possible candidate for further clinical trials involving human subjects in the search for an alternative to cataract surgery.

The parameters investigated in most of the studies assessed bordered on a reduction in oxidative stress markers and an increase in reducing mediators when various agents are administered to combat cataract in animal and human lens. Not all agents function in the same way to inhibit onset and progression of cataract, but it is clear that a combination therapy involving different pathways properly harnessed for the purpose may be the key to a possible alternative to cataract surgery using pharmacotherapy.

Some preparations have been available in many parts of the world that have claimed to cure cataract but no scientific evidence has been adduced to support these claims. A lot of work remains to be done to establish a cause-effect relationship between any agents in human subjects and reduction in lens opacity and progression of age-related cataract.

## RECOMMENDATION

More longitudinal random controlled trials are needed with human subjects before we can scratch the surface in the quest for a therapeutic solution to cataract. Developed and developing countries will benefit tremendously from the reduction in the public health challenges posed by cataract and its implications in both regions. Developed nations will save more money while developing ones will save more people from going blind. Affordable healthcare is only effective when rich and poor nations have equitable access to it.

Dubois and Bastawrous surmised it succinctly in the Cochrane Database Systematic review,

"*Future studies should be randomized, double-masked, placebo-controlled trials with standardized quality of life outcomes and validated outcome measures in terms of visual acuity, contrast sensitivity and glare, and large enough to detect adverse effects.*"[78]

This is a call for more clinical trials and quasi-experiments to unravel a possible solution to the scourge of cataract blindness in developing and under-developed nations around the world and ease the public health burden that it represents in these areas.

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78 Dubois VD, Bastawrous A. N-acetylcarnosine (NAC) drops for age-related cataract. Cochrane Database Syst Rev. 2017;2(2):CD009493. doi:10.1002/14651858.CD009493.pub2.