

Reactive Oxygen Species and eye aging in Cataracts through biomolecular mechanisms

Abstract

The cataractogenesis process and the novel mechanisms involved in its progression make us question that the only solution today presented for its resolution, is through a surgical procedure. The unveiling of such interesting and intricate machinery in the lens opacification, occupies not only ophthalmologists field, but also biology, molecular and biochemistry areas. The animal models, experimental and theoretically, have done their best try to present what appears to be an irreparable and unstoppable process nowadays. The crystalline lens opacification is a chronic and progressively damage due to the lost of balance between the production and elimination of free reactive oxygen species (ROS), the attempts to stop or slow down this overproduction or lack of elimination lie in study material from disciplines as complex as cancer pathways. The execution of this review article was possible through metasearch engines like: Wiley Online library, EBSCO, Cochrane, Clinical key and MEDLINE PubMed (National Library of Medicine, National Institutes of Health), to retrieve studies from January 2021 to January 2022, following PRISMA guidelines, with special affinity to systematic reviews and met-analysis. MeSH Terms associated from "Cataract AND Reactive Oxygen Species". This work constitutes an integral cataractogenesis view in the development of future therapeutic scopes. The world population especially in Europe is aging at a rapid rate, in this sense is necessary to consider a root potential solution and not palliative strategies in ophthalmology for the next generations. The compendium of procedures presented already supposed to open a new panorama to a clearer world, a world without senile cataracts. Time is vision.

Key-words: *Cataractogenesis; Reactive Oxygen Species; Molecular biology; Biochemistry.*

INTRODUCTION

The cataractogenesis process and the novel mechanisms involved in its progression make us question that the only solution today presented for its resolution, is through a surgical procedure. The unveiling of such interesting and intricate machinery in the lens opacification, occupies not only ophthalmologists field, but also biology, molecular and biochemistry areas. The animal models, experimental and theoretically, have done their best try to present what appears to be an irreparable and unstoppable process nowadays.

The crystalline lens opacification is a chronic and progressively damage due to the lost of balance between the production and elimination of free reactive oxygen species (ROS), the attempts to stop or slow down this overproduction or lack of elimination lie in study material from disciplines as complex as cancer pathways. [1]

METHODOLOGY

Data source

The execution of this review article was possible through metasearch engines like: Wiley Online library, EBSCO, Cochrane, Clinical key and MEDLINE PubMed (National Library of Medicine, National Institutes of Health), to retrieve studies from January 2021 to January 2022, following PRISMA guidelines, with special affinity to systematic reviews and met-analysis. MeSH Terms associated from "Cataract AND Reactive Oxygen Species". Fig1.

- Comment [H1]: Remove comma
- Comment [H2]: Remove comma
- Comment [H3]: Add article the
- Comment [H4]: Add comma
- Comment [H5]: Remove a
- Comment [H6]: damaged
- Comment [H7]: loss
- Comment [H8]: remove colon
- Comment [H9]: capitalize initial
- Comment [H10]: add a
- Comment [H11]: correct spelling
- Comment [H12]: change preposition with

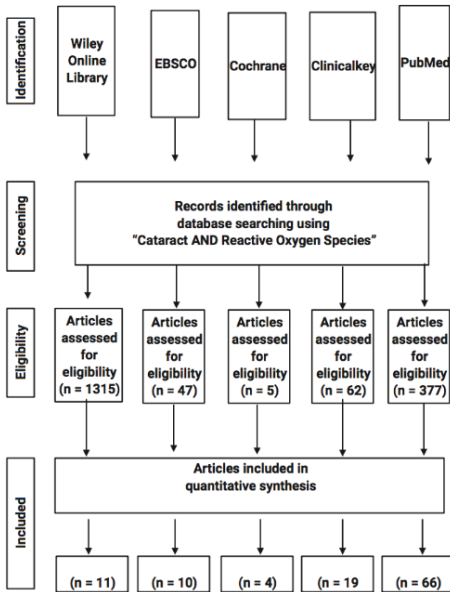


Fig.1 Flow diagram of the literature research.

UNWRAPPING CATARACTS

Cataract has multicausal etiologies, the most common is age related, understandably due to sustained damage to this organ; at the same time responsible for 65.2 million cases, worldwide in first world countries, which made them the leading cause of blindness preventable after 50 years of age, as stated by the World Health Organization and annually around 26 million surgeries.

It's almost odd to Ophthalmologist, talking or reading about biochemistry, molecules and biology; perhaps it is fundamental to every single professional of the eyes and enhanced to microsurgeries that works with cataracts to be aware in the basics of this topic. In the year 1954 was proved the presence of free radicals with the used of resonance spectroscopy, which later other authors dared to think what we know today was not wrong, about peroxide chain reactions would catalyze oxidative stress in vivo. The most power endogenous antioxidant is the mitochondria, but was firstly exposed after 1970. [1-3]

The perfect machinery of human natural lens is absence of organelles and mitochondria is locked to the epithelial cells, consuming almost ninety per cent of the complete oxygen consumption, practically the lens is hypoxic, calculated to be 3 mmHg (~0.4%); at the end 0.2-2% of the oxygen is destiny to produce superoxide and stimulates the respiratory chain oxidative phosphorylation; definitely meaningful to be able to describe the new potential solutions. [4-5]

The Reactive Oxygen Species (ROS) are produce due chronic response as aging, ischemia, toxicity and other factors, the most relevant exponents are: oxygen (O₂), hydrogen peroxide (H₂O₂), hydroxide (-OH), Peroxynitrite (-ONOO₂). In the other hand, the natural defense process is called REDOX (oxidation-reduction), which common element of work is transferring electrons between chemical species, the most representatives: catalase, glutathione and superoxide dismutase (SOD). [6-7]

THE MATHEMATICS BEHIND THE CATARACTS

In cataracts the excess accumulation of ROS specifically units of alfa crystalline, subunits alfa A and alfa B (αA-αB) were documented in lenses of mammals in high concentrations. A common mechanism pathway of the production of singlet dd

Comment [H13]: correct word

Comment [H14]: add comma

Comment [H15]: work

Comment [H16]: use

Comment [H17]: powerful

Comment [H18]: remove comma

Comment [H19]: first

Comment [H20]: add the

Comment [H21]: add an

Comment [H22]: correct spelling

Comment [H23]: remove

Comment [H24]: change word to meant

Comment [H25]: produced

Comment [H26]: add to

Comment [H27]: add comma

Comment [H28]: change to On

Comment [H29]: add in

Comment [H30]: add a

Comment [H31]: elements

Comment [H32]: add comma

commaoxygen energy was calculated and associated using the formula of Eyring–Polanyi equation, which represent the changes between chemical reactions with alterations of temperature.

Comment [H33]: represents

The Arrhenius equation is based on empirical statistical mechanical justification, but without the use of stereochemistry (A), $A=(e/h) kBT \exp(\Delta S^\ddagger/R)$; developed as k = reaction rate constant or coefficient, that quantifies the rate and direction of the chemical reaction; T = absolute temperature (Kelvin or Rankine); ΔH^\ddagger = enthalpy of activation, the complex of higher energy, reactant can convert into products or revert to reactants; R = gas constant, as the universal energy per temperature increment per mole; k_B =Boltzmann constant, for the dimensions of energy divided by temperature (biochemical entropy), when the tendency of natural systems measure the degree of disorder; E_{act} as activation energy; e = the natural logarithm base, mathematical constant equals to 2.718281828459, namely also as $\log x$; h = Planck's constant, related to the mass frequency and mass energy equivalence $6.62607015 \times 10^{-34}$ Joule/Hz; ΔS^\ddagger : entropy of activation, resume as the reactants change from their initial state to the activated state. [8-11]

Comment [H34]:

Comment [H35]: Add hyphen

With the final formula developed like this: $\Delta H^\ddagger = E_{act} - RT$. The importance of this, relapses that temperature is directly responsible in the production of alfa singlet oxygen (ΔG^\ddagger), meaning ROS production. The key number of ΔG^\ddagger range from 92.8–127 kilojoule mol^{-1} at 310 Kelvin, which means a new therapeutic target to induced the opposite state, at least theoretically. [12-15]

Comment [H36]: Remove comma

MOLECULAR BIOLOGY IN LENS OPACITY

The via of the unfolded protein response (UPR), activated previously because of ROS, might restrict the antioxidant modulation and protection of Nrf2-dependent, which modulates DNA dimethylation; In the other hand, homeostasis responsible under physiological conditions is in charge of Keap 1/Nrf2 ARE (antioxidant related elements) and the entire economy of the body at cytoplasmatic level, Nrf2 and Keap 1 are inactive by the negative regulator for each one, with the final mission of REDOX. The rupture of Keap1 and Nrf2 due to oxidative stress, appeared the combination of ARE and Nrf2, with the translocation into the nucleus, ransom proteins and enzymes to fight against ROS; the reversed process is explained by the inhibition of both of them consequently in cell apoptosis. It is now defended by Weifang and colleagues that anti-inflammatory trimetazidine (TMZ) reported a newly antioxidant to reversed the anterior operation with the delayed and protection for the natural lens. Fig. 2. [16-17]

Comment [H37]: Correct spelling

Comment [H38]: Correct spelling

Comment [H39]: Correct spelling

Comment [H40]: reverse

Comment [H41]: delay

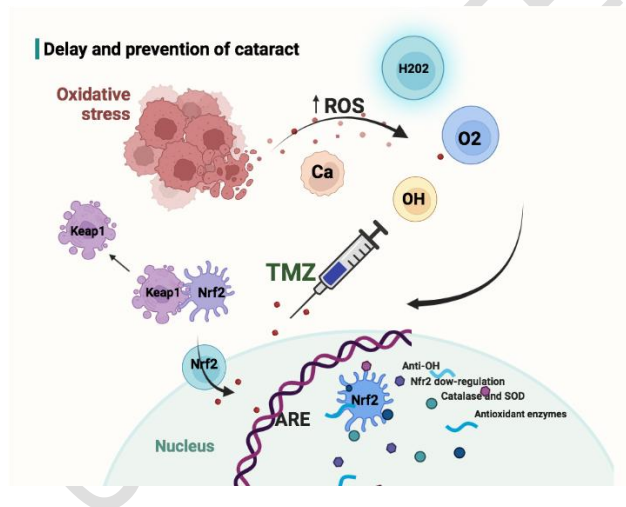


Fig 2. Schematic representation of Trimetazidine (TMZ) prevention and delay in lens opacity via Nrf2/Keap1.

An extensive approach in cataract isn't complete without targeting diabetic cataract mechanisms, as we will now address to. It is well documented that approximately 5 times more frequently diabetic patients will develop cataracts than no diabetics, and the reason behind this conclusion is because of hyperglycaemia levels, which alter the lens epithelial cells

Comment [H42]: cataracts

Comment [H43]: change spelling

(LEC), responsible of the most biochemical activity in metabolism, detoxification, nutrition and transportation of ions, secondary affecting lens opacity due chronicity. [18-22]

Comment [H44]: add to

By itself hyperglycaemia is a potential mechanism of ROS, in cataracts the autophagy cell dysfunction lead to dysregulation of SOD and catalase; experimental models in mice conducted by Xiaomin et al, microtubule associated protein LC3B-I, converts to LC3 B-II bounded to the membrane of autophagosome, in addition to p62 protein, which modulates this lysosome form, concluding that the excess of p62 protein inhibits the autophagy, in the other hand, age related cataract evidence the defect protein degradation in the gene Atg5, in congenital cataracts gene FYCO1 was involved, each of anterior presented with long period of hyperglycaemia in lens epithelial cells autophagy, making a vicious circle with the production of ROS due to hyperglycaemia and the exceeded capacity of the lens to REDOX imbalance. [23-27]

Comment [H45]: correct spelling

Comment [H46]: add the

Comment [H47]: add hyphen

Comment [H48]: add comma

Comment [H49]: add article

Comment [H50]: correct spelling

Comment [H51]: correct spelling

Comment [H52]: remove

The potential solution that might brawl autophagy activity inhibition was Rapamycin, which increased the stress markers reversing ROS. In the following years will consolidate and further clinical trials must point to encouraging final conclusions. [28-31]

Comment [H53]: change wording to other

Comment [H54]: explored

Comment [H55]: add article a

However another mechanisms intricate are needed to be explore; pyroptosis is a form of lytic programmed cell death, highly associated with inflammation due to the rupture of pro-inflammatory cells content, not only in cataracts formation, perhaps pathogen infections, bacteria's, apoptosis are linked to REDOX. The participation of the expression of caspase-1 and interleukin (IL-1B) in the anterior capsule cataract formation, increased in the LEC induced previously with hydrogen peroxide, relevant because they are today's material to delimit caspase 1 as the first caspase cell in mammals to be clearly identified to be enrolled with apoptosis, mediating pro-inflammatory pyroptosis, secondary to external or internal aggressions. [32-43]

Comment [H56]: remove

Comment [H57]: correct spelling

Recent immunochemistry works light up new pathways and processes that in the nearly past years were just lucubrated. This is the case of Rho associated kinase (ROCK) build by protein serine, threonine kinase, family of protein kinase (PKA, PKG, PKC), with 2 domains, important both for regulating adhesion and apoptosis under stress habits; furthermore p53 also known as the guardian of the genome, with highly sense of notifying damage in DNA, has a protective response all around cell metabolism, this two associations ROCK1 and p53 coexist in cytoplasm and both expressions expand by H2O2 and moreover ROCK1 mediated p53 phosphorylation up regulation exactly at serine 15 level, made this relevant because of the cooperation between ROCK1/p53 signaling pathway apoptosis, working directly in the lens epithelial cells. [44-48]

Comment [H58]: add hyphen

Comment [H59]: built

Comment [H60]: add article

Comment [H61]: change adverb

Comment [H62]: add the

Comment [H63]: add hyphen

In the other hand, ROCK inhibition was associated with other useful benefits around ophthalmological fields, as glaucoma treatment, drops like netarsudil, which might explain the same regulated factors in different cell cycles. [49-52]

Comment [H64]: On

Comment [H65]: such as

Comment [H66]: ??

Moreover novel studies in microRNA's played a fundamental role in the pathogenesis not only in cataracts, but in Ophthalmology discipline, etiologist involved like macular degeneration, retinoblastoma, glaucoma and pterygium for mentioning some, this non coding molecules have specific participation downregulating translational processes, like apoptosis cell proliferation and differentiation; one of the most relevant is MIR-182-5p, mainly due interaction in LEC, delaying apoptosis with NOX4 (nicotinamide adenine dinucleotide phosphate oxidase subunit 4) directly responsible in ROS source formation, p38 protein and MAPK (mitogen activated protein kinase) pathway. [53-57]

Comment [H67]: Add comma

Comment [H68]: Remove comma

Comment [H69]: Add the

Comment [H70]: Change determiner

Comment [H71]: Add hyphen

The key role of MIR-182-5p against ROS is inhibiting NOX4 articulation and also p38 MAPK route; this anti-apoptotic and anti-oxidative process emerges as new therapeutic target for tomorrow clinical applications. [58-61]

Comment [H72]: Add a

Comment [H73]: tomorrow's

Comment [H74]: add hyphen

In addition to microRNA's theory, microRNA-378a (miR378a) is involved in tumor suppressive role, mostly succeeded studies because of colorectal and breast cancer, but what association might interfere in cataract formation? As we have developed throughout the text, metabolism of O2 and H2O2 could be blocked by this miR378a PI3K/AKT (phosphatidylinositol 3 kinase and protein kinase) that played a critical aspect in growth and cell survival pathway. In vitro experiments, miR378a reduce the expression of SOD, while inhibition of miR378a promoted SOD in the gene expression, regulating ROS levels.

Comment [H75]: add the

The axis of PI3K/AKT was directly involved in miR378a regulation, specifically in proliferation and apoptosis in LEC. We can conclude because of this that ROS levels downregulated PI3K/AKT. [62]

Therefore antioxidants therapies are because of the anterior exposed, revealing also new potentials; in this sense caffeine was compared to glutathione (GSH) and ascorbic acid, because of the potent antioxidant induction; caffeine namely 1,3,7 trimethylxanthine is found in many different presentations, this alkaloid works as a protective antioxidant, scavenger ROS, mostly hydroxyl radicals, specifically because of the interaction with ultraviolet (UV) light, preventing Fenton's reaction, as result of the creation of hydroxyl radicals from hydrogen peroxide and iron, this is a similar process inside human lens, participating with thermogenesis as we already develop, for how available only in animal models, consisting in the reduction of the mass ratio lens. [63-65]

Comment [H76]: exposure

Comment [H77]: add comma

Comment [H78]: add comma

ARTIFICIAL INTELLIGENCE AS A SUBSTITUTE FOR OUR SENSES

The advancement of technology takes us to deep learning and machine learning field, in one word artificial intelligence, the area with most succeed is diagnosis, particular screening cataracts, where automatization routine processes in nuclear ones are not well graded in slit lamp, artificial intelligence makes not LOCSIII (lens opacity classification system), but Wisconsin grading system better for posterior subcapsular cataracts and in this curse of action, stake out other therapeutic possibilities. [66-67]

Comment [H79]: add article

Comment [H80]: correct

As stated from David Gems and colleagues in the Institute of Healthy Aging and Research department of Genetics from London 2022, we need to look at aging in a new perspective, as a late life disease, opening doors to diligent targets in fields corresponding to ecological factors (epigenetic), viruses, bacteria's, toxins, irradiation, diet, light, stress, genetic factors as the inherited mutations, accumulative mechanisms as the probabilistic versus the regular molecular damages, ontogenetic mechanisms, each of this affecting directly lifespan, decanting in senescent pathology disease and because of that cataract age related formation. [68-73]

OXIDATIVE STRESS AS A KEY ELEMENT IN CATARACT FORMATION

One more interesting pathway for the regulation of REDOX process in human lens is peroxiredoxin 6 (Prdx6), an enzyme which ability to reduce peroxides (REDOX sensors), exact mechanisms are unveiling, but what we know today is Prdx6 diminish because of aging or directly ROS excess, the virtuous activity of Prdx6 stimulates phospholipase A2, from the NADH (Nicotinamide Adenine Dinucleotide) oxidase, making the ambivalence action of protecting or harming the eye lens. [74-77]

Comment [H81]: add article

Comment [H82]: add article

Comment [H83]: change word to unveiled

At the end of the day, researchers proposed exogenous Prdx6 delivery, routing it with a trans activator of transcription domain technique, facilitating the entrance to cells, specifically to LEC mediated by tumor growth factor beta (TGF-β), delaying cataractogenesis. [78-80]

Comment [H84]: correct spelling

Comment [H85]: add hyphen

Substitute nature plant treatment mechanisms are distinguished, like curcumin that utilize lens epithelium cells to upregulate Prdx6 expression. Nevertheless Prdx6 is not solely responsible, further investigations in this field are needed to be run, because signaling activity in peroxiredoxin family are not shared between them, subunit 6 in mammals are the most advanced in eye pathologies. [81]

Comment [H86]: utilizes

Comment [H87]: add comma

Comment [H88]: is

In addition DNA damaged as we already stated, is fully associated with REDOX and ROS but, the noncoding RNA (ncRNA) which are molecules with functional regulation system of the gene expression, participates also in epigenetic processes, going since gene silencing, remodeling chromatin, histone modification and methylation; when we set long ncRNA (lncRNA) we described transcripts longer than 200 nucleotides, most of them we still don't know how they behave. [82-85]

Comment [H89]: add the

Comment [H90]: add comma

Comment [H91]: damage

Comment [H92]: add article

Comment [H93]: change preposition to through

Comment [H94]: through

Cyran a lncRNA namely OIP5-AS1 works in vivo as an upregulating system, with the capacity of renewal embryonic stem cells, modulating miR7 MicroRNAs (miRNAs, miR), capable of regulating post-transcriptional gene expressions; disproportion in the miRNA network have been associated with the development of many pathological conditions and diseases, including not only cataracts, but cancer. [86-89]

Comment [H95]: has

Comment [H96]: remove comma

The exceed expression of OIP5-AS1 and POLG (DNA polymerase subunit gamma), an enzyme in charge of coding the catalytic subunit of mitochondrial DNA polymerase, lead to endogenous apoptotic pathway, with common route cell death, this are suspiciously regulators of cataract age related formation; when in the axis of OIP5-AS1/POLG double knockdown was performed, it wasn't directly cell fate impact. [90-94]

Comment [H97]: exceeded

Comment [H98]: leading

Comment [H99]: is

Worldwide up to-date on the subject deals with nanoparticles, which include small ranges of particles between 1 to 100 nanometers in size. This is the case of CeO₂ NPs (cerium oxide nanoparticles), as a promising biomaterial with tremendous catalytic properties in REDOX. In vitro models (preclinical) was used as an artificial enzyme, not only in the eyes, but alleviating inflammation of neuroglia cells in Alzheimer, mitigating vascular strokes preventing blood barrier damage. Novel models suggest attenuated choroidal neovascularization in age related macular degeneration. [95]

Comment [H100]: add hyphen

The alliance of CeO₂ NPs and biodegradable thermosensitive polymer, poly-dl-lactide-co-glycolide-b-ethylene glycol-b-dl-lactide-co-glycolide (PLGA-PEG-PLGA), with pivotal function of maintaining transparency as an antioxidant with glycation inhibitor for REDOX vicious cycle. In vivo exact mechanism still can't be clarified, but every single path brings us closer to the truth. [96-110]

Comment [H101]: were

Comment [H102]: remove comma

Comment [H103]: change noun form

Comment [H104]: add hyphen

Comment [H105]: the

Human fascinating genome code in fact is in control of promoters and regulator patterns hopefully to open new tools and doors for tomorrow a new dawn for cataracts.

Comment [H106]: remove

CONCLUSION

This work constitutes an integral cataractogenesis view in the development of future therapeutic scopes. The world population especially in Europe is aging at a rapid rate, in this sense is necessary to consider a root potential solution and not palliative strategies in ophthalmology for the next generations. The compendium of procedures presented already supposed to open a new panorama to a clearer world, a world without senile cataracts. Time is vision.

CONSENT INFORM

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

REFERENCES

1. Roy J, Galano J, Durand T, Le Guennec J, Chung- Yung Lee J. Physiological role of reactive oxygen species as promoters of natural defenses. *FASEB j* 2017;31:3729–45. <https://doi.org/10.1096/fi.201700170r>.
2. Jing R, Ma B, Qi T, Hu C, Liao C, Wen C, et al. Long Noncoding RNA OIP5-AS1 Promotes Cell Apoptosis and Cataract Formation by Blocking POLG Expression Under Oxidative Stress. *Invest Ophthalmol Vis Sci* 2020;61:3. <https://doi.org/10.1167/iovs.61.12.3>.
3. Achete de Souza G, de Marqui SV, Matias JN, Guiguer EL, Barbalho SM. Effects of Ginkgo biloba on Diseases Related to Oxidative Stress. *Planta Med* 2020;86:376–86. <https://doi.org/10.1055/a-1109-3405>.
4. Du B, Zheng J-L, Huang L-Y, Zhang H, Wang Q, Hong Y-R, et al. Protective Effect and Mechanism of Bone Morphogenetic Protein-4 on Apoptosis of Human Lens Epithelium Cells under Oxidative Stress. *BioMed Research International* 2021;2021:1–10. <https://doi.org/10.1155/2021/8109134>.
5. Periyasamy P, Shinohara T. Age-related cataracts: Role of unfolded protein response, Ca²⁺ mobilization, epigenetic DNA modifications, and loss of Nrf2/Keap1 dependent cytoprotection. *Progress in Retinal and Eye Research* 2017;60:1–19. <https://doi.org/10.1016/j.preteyeres.2017.08.003>.
6. Natarajan SB, Hwang J-W, Kim Y-S, Kim E-K, Park P-J. Ocular promoting activity of grape polyphenols—A review. *Environmental Toxicology and Pharmacology* 2017;50:83–90. <https://doi.org/10.1016/j.etap.2016.12.004>.
7. Honisch C, Hussain R, Siligardi G, Ruzza P. Influence of small molecules on the photo- stability of water soluble porcine lens proteins. *Chirality* 2020;32:611–8. <https://doi.org/10.1002/chir.23210>.
8. Rumping L, Tessadori F, Pouwels PJW, Vringer E, Wijnen JP, Bhogal AA, et al. GLS hyperactivity causes glutamate excess, infantile cataract and profound developmental delay. *Human Molecular Genetics* 2018;28:96–104. <https://doi.org/10.1093/hmg/ddy330>.
9. Gunathilake KDPP, Ranaweera KKDS, Rupasinghe HPV. Analysis of rutin, β- carotene, and lutein content and evaluation of antioxidant activities of six edible leaves on free radicals and reactive oxygen species. *J Food Biochem* 2018;42. <https://doi.org/10.1111/jfbc.12579>.
10. Kim H-R, Kim S, Lee S-W, Sin H-S, Kim S-Y. Protective Effects of Fermented Paprika (*Capsicum annuum* L.) on Sodium Iodate-Induced Retinal Damage. *Nutrients* 2020;13:25. <https://doi.org/10.3390/nu13010025>.
11. Qi D, Wang M, Zhang D, Li H. Tanshinone IIA protects lens epithelial cells from H₂O₂- induced injury by upregulation of lncRNA ANRIL. *J Cell Physiol* 2019;234:15420–8. <https://doi.org/10.1002/jcp.28189>.
12. Gorni D, Finco A. Oxidative stress in elderly population: A prevention screening study. *Aging Med* 2020;3:205–13. <https://doi.org/10.1002/agm2.12121>.

13. Qiu X, Rong X, Yang J, Lu Y. Evaluation of the antioxidant effects of different histone deacetylase inhibitors (HDACis) on human lens epithelial cells (HLECs) after UVB exposure. *BMC Ophthalmol* 2019;19. <https://doi.org/10.1186/s12886-019-1056-7>.
14. Petrou AL, Terzidaki A. A meta-analysis and review examining a possible role for oxidative stress and singlet oxygen in diverse diseases. *Biochemical Journal* 2017;474:2713–31. <https://doi.org/10.1042/bcj20161058>.
15. 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. <https://doi.org/10.1186/s12886-018-0711-8>.
16. Dubois VD-P, Bastawrous A. N-acetylcarnosine (NAC) drops for age-related cataract. *Cochrane Database of Systematic Reviews* 2011. <https://doi.org/10.1002/14651858.cd009493>.
17. Van Vliet T, Casciaro F, Demaria M. To breathe or not to breathe: Understanding how oxygen sensing contributes to age-related phenotypes. *Ageing Research Reviews* 2021;67:101267. <https://doi.org/10.1016/j.arr.2021.101267>.
18. Fang W, Ye Q, Yao Y, Xiu Y, Gu F, Zhu Y. Protective Effects of Trimetazidine in Retarding Selenite-Induced Lens Opacification. *Current Eye Research* 2019;44:1325–36. <https://doi.org/10.1080/02713683.2019.1633359>.
19. Periyasamy P, Shinohara T. Age-related cataracts: Role of unfolded protein response, Ca²⁺ mobilization, epigenetic DNA modifications, and loss of Nrf2/Keap1 dependent cytoprotection. *Progress in Retinal and Eye Research* 2017;60:1–19. <https://doi.org/10.1016/j.preteyeres.2017.08.003>.
20. Weikel KA, Garber C, Baburins A, Taylor A. Nutritional modulation of cataract. *Nutr Rev* 2013;72:30–47. <https://doi.org/10.1111/nure.12077>.
21. Gong W, Zhu G, Li J, Yang X. LncRNA MALAT1 promotes the apoptosis and oxidative stress of human lens epithelial cells via p38MAPK pathway in diabetic cataract. *Diabetes Research and Clinical Practice* 2018;144:314–21. <https://doi.org/10.1016/j.diabres.2018.06.020>.
22. Thompson B, Chen Y, Davidson EA, Garcia-Milian R, Golla JP, Apostolopoulos N, et al. Impaired GSH biosynthesis disrupts eye development, lens morphogenesis and PAX6 function. *The Ocular Surface* 2021;22:190–203. <https://doi.org/10.1016/j.jtos.2021.08.010>.
23. Chua SYL, Luben RN, Hayat S, Broadway DC, Khaw K-T, Warwick A, et al. Alcohol Consumption and Incident Cataract Surgery in Two Large UK Cohorts. *Ophthalmology* 2021;128:837–47. <https://doi.org/10.1016/j.ophtha.2021.02.007>.
24. Khan AU, Khan AU, Li B, Mahnashi MH, Alyami BA, Alqahtani YS, et al. Biosynthesis of silver capped magnesium oxide nanocomposite using *Olea cuspidata* leaf extract and their photocatalytic, antioxidant and antibacterial activity. *Photodiagnosis and Photodynamic Therapy* 2021;33:102153. <https://doi.org/10.1016/j.pdpdt.2020.102153>.
25. Hajarnavis AM, Bulakh PM. Anticataract effects of *S. cumini* and *A. marmelos* on goat lenses in an experimental diabetic cataract model. *Journal of Ayurveda and Integrative Medicine* 2020;11:421–5. <https://doi.org/10.1016/j.jaim.2019.08.001>.
26. Yoon JJ, Danesh-Meyer HV. Caffeine and the eye. *Survey of Ophthalmology* 2019;64:334–44. <https://doi.org/10.1016/j.survophthal.2018.10.005>.
27. Siegfried CJ, Shui Y-B. Intraocular Oxygen and Antioxidant Status: New Insights on the Effect of Vitrectomy and Glaucoma Pathogenesis. *American Journal of Ophthalmology* 2019;203:12–25. <https://doi.org/10.1016/j.ajo.2019.02.008>.
28. Choudhary R, Bodakhe SH. Magnesium taurate prevents cataractogenesis via restoration of lenticular oxidative damage and ATPase function in cadmium chloride-induced hypertensive experimental animals. *Biomedicine & Pharmacotherapy* 2016;84:836–44. <https://doi.org/10.1016/j.biopha.2016.10.012>.
29. Wojnar W, Zych M, Kaczmarczyk-Sedlak I. Antioxidative effect of flavonoid naringenin in the lenses of type 1 diabetic rats. *Biomedicine & Pharmacotherapy* 2018;108:974–84. <https://doi.org/10.1016/j.biopha.2018.09.092>.
30. Liu X, Zhao X, Cheng R, Huang Y. Autophagy attenuates high glucose-induced oxidative injury to lens epithelial cells. *Bioscience Reports* 2020;40. <https://doi.org/10.1042/bsr20193006>.
31. Impellizzeri D, Siracusa R, Cordaro M, Peritore AF, Gugliandolo E, D'amico R, et al. Protective effect of a new hyaluronic acid -carnosine conjugate on the modulation of the inflammatory response in mice subjected to collagen-induced arthritis. *Biomedicine & Pharmacotherapy* 2020;125:110023. <https://doi.org/10.1016/j.biopha.2020.110023>.
32. Jin X, Jin H, Shi Y, Guo Y, Zhang H. Pyroptosis, a novel mechanism implicated in cataracts. *Mol Med Report* 2018. <https://doi.org/10.3892/mmr.2018.9188>.
33. Liu Y-C, Setiawan M, Ang M, Yam GHF, Mehta JS. Changes in aqueous oxidative stress, prostaglandins, and cytokines: Comparisons of low-energy femtosecond laser-assisted cataract surgery versus conventional phacoemulsification. *Journal of Cataract and Refractive Surgery* 2019;45:196–203. <https://doi.org/10.1016/j.jcrs.2018.09.022>.
34. Rong X, Rao J, Li D, Jing Q, Lu Y, Ji Y. TRIM69 inhibits cataractogenesis by negatively regulating p53. *Redox Biology* 2019;22:101157. <https://doi.org/10.1016/j.redox.2019.101157>.
35. Wishart TFL, Flokis M, Shu DY, Das SJ, Lovicu FJ. Hallmarks of lens aging and cataractogenesis. *Experimental Eye Research* 2021;210:108709. <https://doi.org/10.1016/j.exer.2021.108709>.

36. Babizhayev MA, Yegorov YE. Reactive Oxygen Species and the Aging Eye. *American Journal of Therapeutics* 2016;23:e98–117. <https://doi.org/10.1097/mjt.0b013e3181ea31ff>.
37. Niu L, Liu X, Zhao J, Wang Y, Li Y, Li K, et al. 5-Nitro-2-(3-phenylpropylamino) benzoic acid induces apoptosis of human lens epithelial cells via reactive oxygen species and endoplasmic reticulum stress through the mitochondrial apoptosis pathway. *Int J Mol Med* 2021;47. <https://doi.org/10.3892/ijmm.2021.4892>.
38. Kubo E, Shibata T, Singh D, Sasaki H. Roles of TGF β and FGF Signals in the Lens: Tropomyosin Regulation for Posterior Capsule Opacity. *IJMS* 2018;19:3093. <https://doi.org/10.3390/ijms19103093>.
39. Yang Y, Xu X, Liu Q, Huang H, Huang X, Lv H. Myricetin Prevents Cataract Formation by Inhibiting the Apoptotic Cell Death Mediated Cataractogenesis. *Med Sci Monit* 2020;26. <https://doi.org/10.12659/msm.922519>.
40. Fan X, Monnier VM. Protein posttranslational modification (PTM) by glycation: Role in lens aging and age-related cataractogenesis. *Experimental Eye Research* 2021;210:108705. <https://doi.org/10.1016/j.exer.2021.108705>.
41. 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. <https://doi.org/10.1186/s12886-018-0711-8>.
42. Zhao W-J, Yan Y-B. Increasing susceptibility to oxidative stress by cataract-causing crystallin mutations. *International Journal of Biological Macromolecules* 2018;108:665–73. <https://doi.org/10.1016/j.ijbiomac.2017.12.013>.
43. Hu S, Su D, Sun L, Wang Z, Guan L, Liu S, et al. High-expression of ROCK1 modulates the apoptosis of lens epithelial cells in age-related cataracts by targeting p53 gene. *Mol Med* 2020;26. <https://doi.org/10.1186/s10020-020-00251-6>.
44. Li S, Chen X, Lai W, Hu M, Zhong X, Tan S, et al. Downregulation of SMP30 in senescent human lens epithelial cells. *Molecular Medicine Reports* 2017;16:4022–8. <https://doi.org/10.3892/mmr.2017.7106>.
45. Du S, Shao J, Qi Y, Liu X, Liu J, Zhang F. Long non-coding RNA ANRIL alleviates H₂O₂-induced injury by up-regulating microRNA-21 in human lens epithelial cells. *Aging* 2020;12:6543–57. <https://doi.org/10.18632/aging.102800>.
46. Xu D, Zhu H, Fu Q, Xu S, Sun W, Chen G, et al. Ketamine delays progression of oxidative and damaged cataract through regulating HMGB-1/NF- κ B in lens epithelial cells. *Immunopharmacology and Immunotoxicology* 2018;40:303–8. <https://doi.org/10.1080/08923973.2018.1478851>.
47. Hernebring M, Adelöf J, Wiseman J, Petersen A, Zetterberg M. H₂O₂-induced cataract as a model of age-related cataract: Lessons learned from overexpressing the proteasome activator PA28 α β in mouse eye lens. *Experimental Eye Research* 2021;203:108395. <https://doi.org/10.1016/j.exer.2020.108395>.
48. Yang H, Cui Y, Tang Y, Tang X, Yu X, Zhou J, et al. Cytoprotective role of humanin in lens epithelial cell oxidative stress-induced injury. *Mol Med Rep* 2020;22:1467–79. <https://doi.org/10.3892/mmr.2020.11202>.
49. Qi L, Zhou Y, Li W, Zheng M, Zhong R, Jin X, et al. Effect of Moringa oleifera stem extract on hydrogen peroxide-induced opacity of cultured mouse lens. *BMC Complement Altern Med* 2019;19. <https://doi.org/10.1186/s12906-019-2555-z>.
50. Sun Y, Rong X, Li D, Lu Y, Ji Y. NF- κ B/Cartilage Acidic Protein 1 Promotes Ultraviolet B Irradiation-Induced Apoptosis of Human Lens Epithelial Cells. *DNA and Cell Biology* 2020;39:513–21. <https://doi.org/10.1089/dna.2019.5086>.
51. Liu H, Smith AJ, Ball SS, Bao Y, Bowater RP, Wang N, et al. Sulforaphane promotes ER stress, autophagy, and cell death: implications for cataract surgery. *J Mol Med* 2017;95:553–64. <https://doi.org/10.1007/s00109-016-1502-4>.
52. Li Z-N, Ge M-X, Yuan Z-F. MicroRNA-182-5p protects human lens epithelial cells against oxidative stress-induced apoptosis by inhibiting NOX4 and p38 MAPK signalling. *BMC Ophthalmol* 2020;20. <https://doi.org/10.1186/s12886-020-01489-8>.
53. Huang Y, Ye Z, Yin Y, Ma T, Zhang Q, Shang K, et al. Cataract formation in transgenic HO-1 G143H mutant mice: Involvement of oxidative stress and endoplasmic reticulum stress. *Biochemical and Biophysical Research Communications* 2021;537:43–9. <https://doi.org/10.1016/j.bbrc.2020.12.071>.
54. Jin X, Jin H, Shi Y, Guo Y, Zhang H. Long Non-Coding RNA KCNQ1OT1 Promotes Cataractogenesis via miR-214 and Activation of the Caspase-1 Pathway. *Cell Physiol Biochem* 2017;42:295–305. <https://doi.org/10.1159/000477330>.
55. Mei L, Yan H, Wang S, Guo C, Zheng X, Yan B, et al. Upregulation of miR-630 Induced by Oxidative Damage Resists Cell Migration Through Targeting ALCAM in Human Lens Epithelium Cells. *Current Eye Research* 2019;45:153–61. <https://doi.org/10.1080/02713683.2019.1656748>.
56. Das SJ, Wishart TFL, Jandeleit-Dahm K, Lovicu FJ. Nox4-mediated ROS production is involved, but not essential for TGF β -induced lens EMT leading to cataract. *Experimental Eye Research* 2020;192:107918. <https://doi.org/10.1016/j.exer.2020.107918>.
57. Heruye S, Maffofofu N. LN, Singh NU, Munt D, Njie-Mbye Y-F, Ohia SE, et al. Standardization of a new method for assessing the development of cataract in cultured bovine lenses. *Journal of Pharmacological and Toxicological Methods* 2019;98:106592. <https://doi.org/10.1016/j.vascn.2019.106592>.

58. Wang Z, Su D, Sun Z, Liu S, sun L, Li Q, et al. MDM2 phosphorylation mediates H₂O₂-induced lens epithelial cells apoptosis and age-related cataract. *Biochemical and Biophysical Research Communications* 2020;528:112–9. <https://doi.org/10.1016/j.bbrc.2020.05.060>.
59. Ma Y, Liu F, Xu Y. Protective Effect of β -Glucogallin on Damaged Cataract Against Methylglyoxal Induced Oxidative Stress in Cultured Lens Epithelial Cells. *Med Sci Monit* 2019;25:9310–8. <https://doi.org/10.12659/msm.917869>.
60. Kaczmarczyk-Sedlak I, Folwarczna J, Sedlak L, Zych M, Wojnar W, Szumińska I, et al. Effect of caffeine on biomarkers of oxidative stress in lenses of rats with streptozotocin-induced diabetes. *Aoms* 2019;15:1073–80. <https://doi.org/10.5114/aoms.2019.85461>.
61. Liu Y, Li H, Liu Y. microRNA-378a Regulates the Reactive Oxygen Species (ROS)/Phosphatidylinositol 3-Kinases (PI3K)/AKT Signaling Pathway in Human Lens Epithelial Cells and Cataract. *Med Sci Monit* 2019;25:4314–21. <https://doi.org/10.12659/msm.916881>.
62. Hong Y, Sun Y, Rong X, Li D, Lu Y, Ji Y. Exosomes from adipose-derived stem cells attenuate UVB-induced apoptosis, ROS, and the Ca²⁺ level in HLEC cells. *Experimental Cell Research* 2020;396:112321. <https://doi.org/10.1016/j.yexcr.2020.112321>.
63. Shi W, Riquelme MA, Gu S, Jiang JX. Connexin hemichannel mediates glutathione transport and protects lens fiber cells against oxidative stress. *Journal of Cell Science* 2018. <https://doi.org/10.1242/jcs.212506>.
64. Lledó VE, Alkozi HA, Sánchez-Naves J, Fernandez-Torres MA, Guzman-Aranguez A. Modulation of aqueous humor melatonin levels by yellow-filter and its protective effect on lens. *Journal of Photochemistry and Photobiology B: Biology* 2021;221:112248. <https://doi.org/10.1016/j.jphotobiol.2021.112248>.
65. Chen X, Xu J, Chen X, Yao K. Cataract: Advances in surgery and whether surgery remains the only treatment in future. *Advances in Ophthalmology Practice and Research* 2021;1:100008. <https://doi.org/10.1016/j.aopr.2021.100008>.
66. McMonnies C. Reactive oxygen species, oxidative stress, glaucoma and hyperbaric oxygen therapy. *Journal of Optometry* 2018;11:3–9. <https://doi.org/10.1016/j.optom.2017.06.002>.
67. Gems D. The hyperfunction theory: An emerging paradigm for the biology of aging. *Ageing Research Reviews* 2022;74:101557. <https://doi.org/10.1016/j.arr.2021.101557>.
68. Xu J, Li D, Zheng T, Lu Y. β -amyloid expression in age-related cataract lens epithelia and the effect of β -amyloid on oxidative damage in human lens epithelial cells. *Mol Vis*. 2017 Dec 25;23:1015-1028. PMID: 29386875; PMCID: PMC5757856.
69. Ping X, Cheng Y, Bao J, Shi K, Zou J, Shentu X. KPNA4 is involved in cataract formation via the nuclear import of p53. *Gene* 2021;786:145621. <https://doi.org/10.1016/j.gene.2021.145621>.
70. Li Q, Pan H, Liu Q. MicroRNA-15a modulates lens epithelial cells apoptosis and proliferation through targeting B-cell lymphoma-2 and E2F transcription factor 3 in age-related cataracts. *Bioscience Reports* 2019;39. <https://doi.org/10.1042/bsr20191773>.
71. Zhang J, Yan H, Lou MF. Does oxidative stress play any role in diabetic cataract formation? ----Re-evaluation using a thioltransferase gene knockout mouse model. *Experimental Eye Research* 2017;161:36–42. <https://doi.org/10.1016/j.exer.2017.05.014>.
72. Hu X, Liang Y, Zhao B, Wang Y. Oxyresveratrol protects human lens epithelial cells against hydrogen peroxide-induced oxidative stress and apoptosis by activation of Akt/HO-1 pathway. *Journal of Pharmacological Sciences* 2019;139:166–73. <https://doi.org/10.1016/j.jphs.2019.01.003>.
73. lang S, Chen J. RETRACTED ARTICLE: WRN inhibits oxidative stress-induced apoptosis of human lensepithelial cells through ATM/p53 signaling pathway and its expression is downregulated by DNA methylation. *Mol Med* 2020;26. <https://doi.org/10.1186/s10020-020-00187-x>.
74. Li H, Jiang H, Rong R, Jiang J, Ji D, Song W, et al. Identification of GJA3 p.S50P Mutation in a Chinese Family with Autosomal Dominant Congenital Cataract and Its Underlying Pathogenesis. *DNA and Cell Biology* 2020;39:1760–6. <https://doi.org/10.1089/dna.2020.5605>.
75. Prior HM, Letwin K, Tuininga A, Nguyen M. A Simple Method of Cataract Induction in Adult Zebrafish. *Zebrafish* 2018;15:211–2. <https://doi.org/10.1089/zeb.2017.1533>.
76. Qin Z, Zhang L, Lyu D, Li J, Tang Q, Yin H, et al. Opacification of lentoid bodies derived from human induced pluripotent stem cells is accelerated by hydrogen peroxide and involves protein aggregation. *J Cell Physiol* 2019;234:23750–62. <https://doi.org/10.1002/jcp.28943>.
77. D'Antin JC, Barraquer RI, Tresserra F, Michael R. Prevention of posterior capsule opacification through intracapsular hydrogen peroxide or distilled water treatment in human donor tissue. *Sci Rep* 2018;8. <https://doi.org/10.1038/s41598-018-31178-y>.
78. Zhu L, Li J, Wu D, Li B. The protective effect of beta-casomorphin-7 via promoting Foxo1 activity and nuclear translocation in human lens epithelial cells. *Cutaneous and Ocular Toxicology* 2018;37:267–74. <https://doi.org/10.1080/15569527.2018.1445095>.

79. Nagai N, Ito Y, Shibata T, Kubo E, Sasaki H. A positive feedback loop between nitric oxide and amyloid β (1-42) accelerates mitochondrial damage in human lens epithelial cells. *Toxicology* 2017;381:19–30. <https://doi.org/10.1016/j.tox.2017.02.014>.
80. Wahlig S, Lovatt M, Mehta JS. Functional role of peroxiredoxin 6 in the eye. *Free Radical Biology and Medicine* 2018;126:210–20. <https://doi.org/10.1016/j.freeradbiomed.2018.08.017>.
81. Tu Y, Li L, Qin B, Wu J, Cheng T, Kang L, Guan H. Long noncoding RNA glutathione peroxidase 3-antisense inhibits lens epithelial cell apoptosis by upregulating glutathione peroxidase 3 expression in age-related cataract. *Mol Vis*. 2019 Nov 14;25:734-744. PMID: 31814699; PMCID: PMC6857780.
82. Li L, Fan D-B, Zhao Y-T, Li Y, Yang Z-B, Zheng G-Y. GJA8 missense mutation disrupts hemichannels and induces cell apoptosis in human lens epithelial cells. *Sci Rep* 2019;9. <https://doi.org/10.1038/s41598-019-55549-1>.
83. Zhang M, Cheng K. Long non-coding RNA KCNQ1OT1 promotes hydrogen peroxide-induced lens epithelial cell apoptosis and oxidative stress by regulating miR-223-3p/BCL2L2 axis. *Experimental Eye Research* 2021;206:108543. <https://doi.org/10.1016/j.exer.2021.108543>.
84. Wang S, Guo C, Yu M, Ning X, Yan B, Zhao J, et al. Identification of H₂O₂ induced oxidative stress associated microRNAs in HLE-B3 cells and their clinical relevance to the progression of age-related nuclear cataract. *BMC Ophthalmol* 2018;18. <https://doi.org/10.1186/s12886-018-0766-6>.
85. De-qian K, Yue L, Li L, Guangying Z. Downregulation of Smac attenuates H₂O₂-induced apoptosis via endoplasmic reticulum stress in human lens epithelial cells. *Medicine* 2017;96:e7419. <https://doi.org/10.1097/md.00000000000007419>.
86. Chung I, Hah Y-S, Ju S, Kim J-H, Yoo W-S, Cho H-Y, et al. Ultraviolet B Radiation Stimulates the Interaction between Nuclear Factor of Activated T Cells 5 (NFAT5) and Nuclear Factor-Kappa B (NF- κ B) in Human Lens Epithelial Cells. *Current Eye Research* 2017;42:987–94. <https://doi.org/10.1080/02713683.2016.1270327>.
87. Lu B, Christensen I, Ma L, Wang X, Jiang L, Wang C, et al. miR-24-p53 pathway evoked by oxidative stress promotes lens epithelial cell apoptosis in age-related cataracts. *Mol Med Report* 2018. <https://doi.org/10.3892/mmr.2018.8492>.
88. Bai J, Yang F, Dong L, Zheng Y. Ghrelin Protects Human Lens Epithelial Cells against Oxidative Stress-Induced Damage. *Oxidative Medicine and Cellular Longevity* 2017;2017:1–8. <https://doi.org/10.1155/2017/1910450>.
89. Jing R, Ma B, Qi T, Hu C, Liao C, Wen C, et al. Long Noncoding RNA OIP5-AS1 Promotes Cell Apoptosis and Cataract Formation by Blocking POLG Expression Under Oxidative Stress. *Invest Ophthalmol Vis Sci* 2020;61:3. <https://doi.org/10.1167/iov.61.12.3>.
90. Su D, Hu S, Guan L, Wu X, Shi C, Yang X, et al. Down-regulation of GJA3 is associated with lens epithelial cell apoptosis and age-related cataract. *Biochemical and Biophysical Research Communications* 2017;484:159–64. <https://doi.org/10.1016/j.bbrc.2017.01.050>.
91. Li J, Chen X, Yan Y, Yao K. Molecular genetics of congenital cataracts. *Experimental Eye Research* 2020;191:107872. <https://doi.org/10.1016/j.exer.2019.107872>.
92. Schey KL, Wang Z, Friedrich MG, Garland DL, Truscott RJW. Spatiotemporal changes in the human lens proteome: Critical insights into long-lived proteins. *Progress in Retinal and Eye Research* 2020;76:100802. <https://doi.org/10.1016/j.preteyeres.2019.100802>.
93. Truscott RJW, Friedrich MG. Molecular Processes Implicated in Human Age-Related Nuclear Cataract. *Invest Ophthalmol Vis Sci* 2019;60:5007. <https://doi.org/10.1167/iov.19-27535>.
94. Zhou Y, Li L, Li S, Zhao M, Zhou Q, et al. Autoregenerative redox nanoparticles as an antioxidant and glycation inhibitor for palliation of diabetic cataracts. *Nanoscale* 2019;11:13126–38. <https://doi.org/10.1039/c9nr02350j>.
95. Schey KL, Wang Z, Friedrich MG, Garland DL, Truscott RJW. Spatiotemporal changes in the human lens proteome: Critical insights into long-lived proteins. *Progress in Retinal and Eye Research* 2020;76:100802. <https://doi.org/10.1016/j.preteyeres.2019.100802>.
96. Zhang K, Zhu X, Lu Y. The Proteome of Cataract Markers: Focus on Crystallins. *Advances in Clinical Chemistry* 2018;179–210. <https://doi.org/10.1016/bs.acc.2018.05.005>.
97. Li Y, Liu X, Xia CH, FitzGerald PG, Li R, Wang J, Gong X. CP49 and filensin intermediate filaments are essential for formation of cold cataract. *Mol Vis*. 2020 Aug 23;26:603-612. PMID: 32913386; PMCID: PMC7479064.
98. Xue M, Ke Y, Ren X, Zhou L, Liu J, Zhang X, et al. Proteomic analysis of aqueous humor in patients with pathologic myopia. *Journal of Proteomics* 2021;234:104088. <https://doi.org/10.1016/j.jprot.2020.104088>.
99. Frankfater C, Bozeman SL, Hsu F-F, Andley UP. Alpha-crystallin mutations alter lens metabolites in mouse models of human cataracts. *PLoS ONE* 2020;15:e0238081. <https://doi.org/10.1371/journal.pone.0238081>.
100. Yanshole VV, Yanshole LV, Snytnikova OA, Tsentalovich YP. Quantitative metabolomic analysis of changes in the lens and aqueous humor under development of age-related nuclear cataract. *Metabolomics* 2019;15. <https://doi.org/10.1007/s11306-019-1495-4>.

101. Jackson D, Malka S, Harding P, Palma J, Dunbar H, Moosajee M. Molecular diagnostic challenges for non-retinal developmental eye disorders in the United Kingdom. *Am J Med Genet* 2020;184:578–89. <https://doi.org/10.1002/ajmg.c.31837>.
102. Pawliczek D, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Graw J, Dalke C. Ionising radiation causes vision impairment in neonatal B6C3F1 mice. *Experimental Eye Research* 2021;204:108432. <https://doi.org/10.1016/j.exer.2020.108432>.
103. Moravikova J, Honzik T, Jadvidzakova E, Zdrahalova K, Kremlikova Pourova R, Korbasova M, et al. Hereditary hyperferritinemia-cataract syndrome in three Czech families: molecular genetic testing and clinical implications. *Journal of American Association for Pediatric Ophthalmology and Strabismus* 2020;24:352.e1-352.e5. <https://doi.org/10.1016/j.jaapos.2020.07.014>.
104. Ragg S, Key M, Rankin F, WuDunn D. The Effect of Molecular Weight on Passage of Proteins Through the Blood-Aqueous Barrier. *Invest Ophthalmol Vis Sci* 2019;60:1461. <https://doi.org/10.1167/iovs.19-26542>.
105. Varadaraj K, Gao J, Mathias RT, Kumari S. C-Terminal End of Aquaporin 0 Regulates Lens Gap Junction Channel Function. *Invest Ophthalmol Vis Sci* 2019;60:2525. <https://doi.org/10.1167/iovs.19-26787>.
106. De Bruyne S, van Schie L, Himpe J, De Somer F, Everaert I, Derave W, et al. A Potential Role for Fructosamine-3-Kinase in Cataract Treatment. *IJMS* 2021;22:3841. <https://doi.org/10.3390/ijms22083841>.
107. Choquet H, Melles RB, Anand D, Yin J, Cuellar-Partida G, Wang W, et al. A large multiethnic GWAS meta-analysis of cataract identifies new risk loci and sex-specific effects. *Nat Commun* 2021;12. <https://doi.org/10.1038/s41467-021-23873-8>.
108. Smith AJO, Eldred JA, Wormstone IM. Resveratrol Inhibits Wound Healing and Lens Fibrosis: A Putative Candidate for Posterior Capsule Opacification Prevention. *Invest Ophthalmol Vis Sci* 2019;60:3863. <https://doi.org/10.1167/iovs.18-26248>.
109. Lázara MV, Arturo PP, Zaylit MO. Participación de las especies reactivas de oxígeno en la formación de catarata. *Revista Cubana de Oftalmología* 2021;34(2):e1018.
110. Wu X, Liu Z, Zhang X, Wang D, Long E, Wang J, et al. Proteomics analysis and proteogenomic characterization of different physiopathological human lenses. *BMC Ophthalmol* 2017;17. <https://doi.org/10.1186/s12886-017-0642-9>.