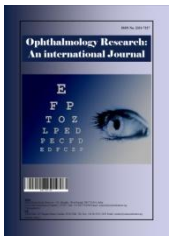

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Reactive Oxygen Species and Eye Aging in Cataracts through Biomolecular Mechanisms

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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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 the 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 chronic and progressively damaged due to the loss 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 a special affinity to systematic reviews and meta-analysis. MeSH Terms associated with "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.

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Keywords: Cataractogenesis; reactive oxygen species; molecular biology; biochemistry.

1. 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].

2. METHODOLOGY

2.1 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 a special affinity to systematic reviews and meta-analysis. MeSH Terms associated from "Cataract AND Reactive Oxygen Species" Fig. 1.

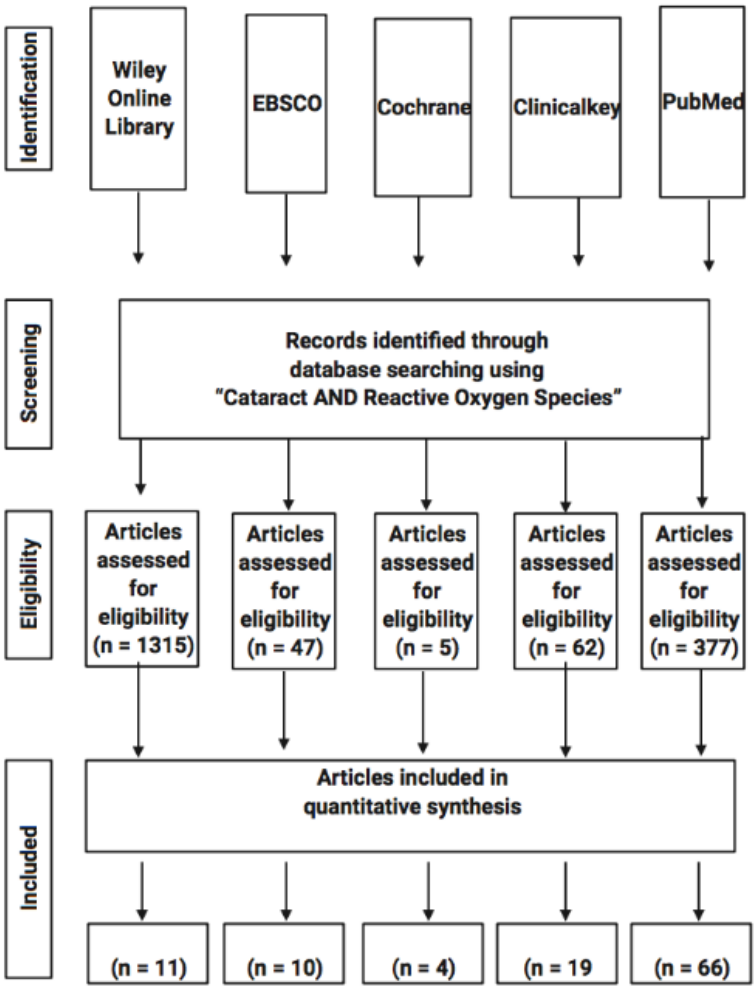

Fig. 1. Flow diagram of the literature research

3. UNWRAPPING CATARACTS

Cataract has multicausal etiologies, the most common is age-relate 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 work with cataracts to be aware in the basics of this topic. In the year 1954 was proved the presence of free radicals with the use 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 powerful endogenous antioxidant is the mitochondria but was first exposed after 1970 [1-3].

The perfect machinery of the human natural lens is an absence of organelles and mitochondria is locked to the epithelial cells, consuming almost ninety percentage 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; meant to be able to describe the new potential solutions [4-5].

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

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

The Arrhenius equation is based on empirical statistical mechanical justification, but without the use of stereochemistry (A), A=(e/h) kBT exp (ΔS≠/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≠ = 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; kB=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 6.62607015×10^{-34} Joule/Hertz; ΔS≠: entropy of activation, resume as the reactants change from their initial state to the activated state [8-11].

With the final formula developed like this: ΔH≠ = E act – RT. The importance of this relapses that temperature is directly responsible in the production of alfa singlet oxygen (ΔG≠), meaning ROS production. The key number of ΔG≠ 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].

5. 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 methylation; on the other hand, homeostasis responsible under physiological conditions is in charge of Keap 1/Nfr2 ARE (antioxidant related elements) and the entire economy of the body at cytoplasmatic level, Nfr2 and Keap 1 are inactive by the negative regulator for each one, with the final mission of REDOX. The rupture of Keap1 and Nfr2 due to oxidative stress, appeared the combination of ARE and Nfr2, 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 reverse the anterior operation with the delay and protection for the natural lens Fig. 2. [16-17].

An extensive approach in cataracts 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 hyperglycemia levels, which alter the lens epithelial cells (LEC), responsible of the most biochemical activity in metabolism, detoxification, nutrition and transportation of ions, secondary affecting lens opacity due to chronicity [18-22].

By itself hyperglycemia 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, microtube associated protein LC3B-I, converts to LC3 B-II bounded to the membrane of the 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 the long period of hyperglycemia in lens epithelial cells autophagy, making a vicious circle with the production of ROS due to hyperglycemia and the exceeded capacity of the lens to REDOX imbalance [23-27].

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 conclusions [28-31].

However other mechanisms intricate are needed to be explored; a 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 identified to be enrolled with apoptosis, mediating pro-inflammatory pyroptosis, secondary to external or internal aggressions [32-43].

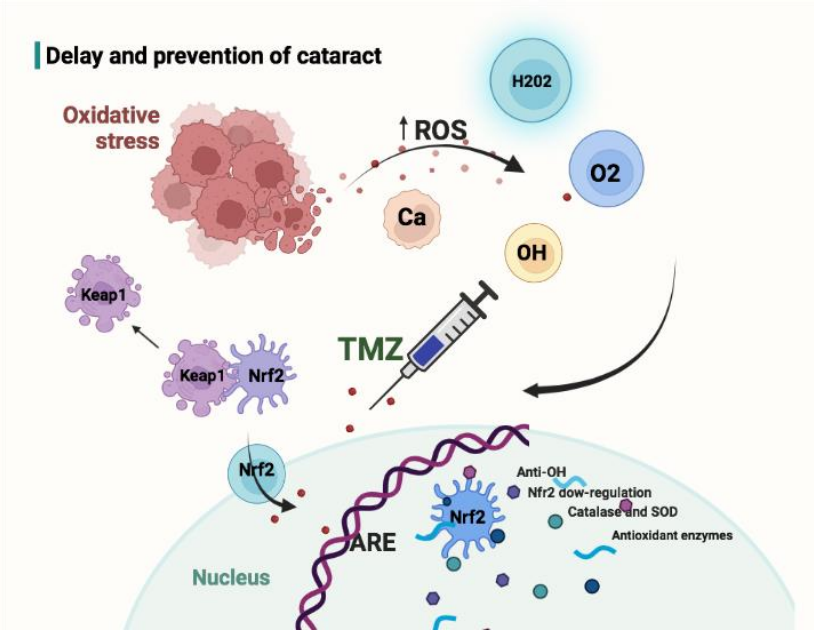

Fig. 2. Schematic representation of Trimetazidine (TMZ) prevention and delay in lens opacity via Nfr2/Keap1

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) built by protein serine, threonine kinase, a 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 particularly sense of notifying damage in DNA, has a protective response all around cell metabolism, this two associations ROCK1 and p53 coexist in the cytoplasm and both expressions expand by H202 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].

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

Moreover, novel studies in microRNA´s played a fundamental role in the pathogenesis not only in cataracts but in the Ophthalmology discipline, etiologist involved like macular degeneration, retinoblastoma, glaucoma and pterygium for mentioning some, the non coding molecules have specific participation down-regulating 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].

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 a new therapeutic target for tomorrow´s clinical applications [58-61].

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 H202 could be blocked by this miR378a PI3K/AKT (phosphatidylinositol 3 kinase and protein kinase) that played a critical aspect in the 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.

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 down-regulated PI3K/AKT [62].

Therefore antioxidants therapies are because of the anterior exposure 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 now, available only in animal models, consisting in the reduction of the mass ratio lens [63-65].

6. 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 the diagnosis, particular screening cataracts, where automatization routine processes in nuclear ones are not well graded in slit lamp, artificial intelligence makes not LOCS-III (Lens Opacity Classification System), but Wisconsin grading system better for posterior sub-capsular cataracts and in this curse of action, stake out other therapeutic possibilities [66-67].

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].

7. OXIDATIVE STRESS AS A KEY ELEMENT IN CATARACT FORMATION

One more interesting pathway for the regulation of the REDOX process in a human lens is peroxiredoxin 6 (Prdx6), an enzyme which ability to reduce peroxides (REDOX sensors), exact mechanisms are unveiled 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].

At the end of the day, researchers proposed exogenous Prdx6 delivery, routing it with an 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].

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

In addition, DNA damage as we already stated, is fully associated with REDOX and ROS but, the noncoding RNA (ncRNA) which are molecules with a functional regulation system of the gene expression, participates also in epigenetic processes, going through 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].

Cyrano a lncRNA namely OIP5-AS1 works in vivo as an up-regulating 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 has been associated with the development of many pathological conditions and diseases, including not only cataracts but cancer [86-89].

The exceeded expression of OIP5-AS1 and POLG (DNA polymerase subunit gamma), an enzyme in charge of coding the catalytic subunit of mitochondrial DNA polymerase, leading to endogenous apoptotic pathway, with common route cell death, this is 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].

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 Ce02 NPs (cerium oxide nanoparticles), as a promising biomaterial with tremendous catalytic properties in REDOX. In vitro models (preclinical) were used as an artificial enzyme, not only in the eyes but alleviating inflammation of neuroglia cells in the Alzheimer disease, mitigating vascular strokes preventing blood barrier damage. Novel models suggest attenuated choroidal neovascularization in age-related macular degeneration [95].

The alliance of Ce02 NPs and biodegradable thermosensitive polymer, poly-dl-lactide-co-glycolide-b-ethylene glycol-b-dl-lactide-co-glycolide (PLGA-PEG-PLGA), with the 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].

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

8. 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

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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